Pharmacological aspects

Pharmacologic treatments for opioid dependence: detoxification and maintenance options

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Detoxification

Although agonist maintenance therapies yield better outcomes for most opioid addicts,[1-3] they continue to seek opioid withdrawal primarily to lower the cost of their habit or as pretreatment before the residential therapeutic community or opioid antagonist maintenance. High relapse rates are probably less a function of withdrawal method and due more to reasons for seeking detoxifica-

While opioid dependence has more treatment agents available than other abused drugs, none are curative. They can, however, markedly diminish withdrawal symptoms and craving, and block opioid effects due to lapses.

The most effective withdrawal method is substituting and tapering methadone or buprenorphine. α-2 Adrenergic agents can ameliorate untreated symptoms or substitute for agonists if not available. Shortening withdrawal by precipitating it with narcotic antagonists has been studied, but the methods are plagued by safety issues or persisting symptoms. Neither the withdrawal agents nor the methods are associated with better long-term outcome, which appears mostly related to post-detoxification treatment.

Excluding those with short-term habits, the best outcome occurs with long-term maintenance on methadone or buprenorphine accompanied by appropriate psychosocial interventions. Those with strong external motivation may do well on the antagonist naltrexone. Currently, optimum duration of maintenance on either is unclear. Better agents are needed to impact the brain changes related to addiction.

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tion, postwithdrawal treatment, or brain changes developed during dependence. Those who complete detoxification tend to have longer times to relapse than dropouts.[4,5]

Clinical issues

Symptom severity is related to the specific narcotic used (short-acting yields more severe withdrawal); amount used; duration of use (at least 2 to 3 weeks, daily); and set and setting factors. Withdrawal phenomena are generally the opposite of acute agonist effects. Withdrawal from heroin begins with anxiety and craving 8 to 12 hours after the last dose, reaches its peak between 36 and 72 hours, and subsides substantially within 5 days. Methadone withdrawal begins at 24 to 36 hours, peaks at 96 to 144 hours, and may last for weeks. Individuals differ markedly, both as to which symptoms are present and their severity.[6] Acute opioid withdrawal symptoms are followed by a protracted abstinence syndrome, including dysphoria, fatigue, insomnia and irritability, for 6 to 8 months.[7]

Withdrawal agents

Methadone

Methadone is orally effective, long-acting—thus producing smoother withdrawal—and safe, if care is taken with initial dosing.
Because 40 mg of methadone has been a fatal dose in some nontolerant individuals, the initial dose should be less, eg, 10 to 20 mg. If withdrawal symptoms are not suppressed within 1 hour, more can be given, but in general the initial dose should not exceed 30 mg, and the total 24-hour dose should not exceed 40 mg the first few days. In a *nontolerant* individual, an initial tolerated dose can become risky if continued beyond 2 days because of rising methadone blood levels.[8] The clinician should be alert for signs of drowsiness or motor impairment.
Physical dependence can be ascertained by: (i) waiting until the patient develops withdrawal signs and symptoms; or (ii) precipitating withdrawal via naloxone (if pregnancy has been ruled out).
After the patient is stabilized, the dosage is gradually reduced, either by decreasing the methadone 5 mg/day until zero dosage is reached, or decreasing 10 mg/day until 10 mg is reached and then by 2 mg/day.[9]
Inpatient methadone substitution and taper is usually accomplished in 5 to 7 days, and has a retention rate of

80%; with outpatient detoxification it takes longer to minimize withdrawal symptoms and to decrease dropout and relapse, but only about 20% complete it.[10] Lingering protracted withdrawal symptoms can be helped by clonidine.

Buprenorphine

The Food and Drug administration (FDA) approved sublingual buprenorphine in 2002 for office-based treatment for detoxification or maintenance of opioid dependence. Buprenorphine is long-acting, safe, and effective by the sublingual route, but may precipitate withdrawal symptoms if given too soon after an opioid agonist. If the patient has withdrawal symptoms and has waited at least 12 hours after short-acting opioids and 36 hours after methadone, buprenorphine usually serves to relieve these symptoms and is less likely to precipitate withdrawal. It may also be useful in emergency department settings.[11]
Heroin detoxification is managed by administering buprenorphine 2 to 4 mg sublingually after the emergence of mild-to-moderate withdrawal. A second dose of buprenorphine 2 to 4 mg may be administered approximately 1 to 2 hours later, depending on the patient's comfort level. Usually a total of 8 to 12 mg of buprenorphine is sufficient the first day. For most patients, a slow taper over a week or so is a safe and well tolerated strategy. Any buprenorphine dose that worsens withdrawal symptoms suggests the buprenorphine dose is too high compared with the level of withdrawal. The symptoms should be treated with clonidine, and further buprenorphine doses withheld for at least 6 to 8 hours. Buprenorphine, even at doses of 16 mg, may not suppress all signs and symptoms of withdrawal if the patient had a very severe habit,[12] but most symptoms respond to adding clonidine 0.1 mg every 4 to 6 hours.
The duration of withdrawal from abrupt buprenorphine cessation is variable even from patient to patient. In one study, about one fifth of the patients maintained on daily buprenorphine 16 mg sublingually for 10 days experienced significant withdrawal symptoms after abrupt stopping.[13] Buprenorphine can be used to transfer patients from methadone maintenance to buprenorphine maintenance or to a drug-free state. The patient needs to be at least in mild withdrawal, and the methadone dose 40 mg or less for at least a week prior to beginning buprenorphine.[14]
Another way of using buprenorphine is for rapid withdrawal. A randomized study in heroin addicts[15] compared

anesthesia-assisted with buprenorphine-assisted detoxification, followed by antagonist induction. The buprenorphine group received a single dose of 8 mg on day 0, none on day 1, and naltrexone on day 2 at 12.5 mg, titrated up to 50 mg/day over 2 days. Symptom severity and retention at 1 month were similar in both groups. Another study also found that prior buprenorphine preparation markedly decreased post procedure morbidity.[16]

A recent systematic review compared buprenorphine to other detoxification strategies.[17] Compared with clonidine, buprenorphine was found to be more effective in ameliorating withdrawal symptoms; patients stayed in treatment longer, especially in outpatient settings, and were more likely to complete withdrawal. When compared with methadone-aided withdrawal, buprenorphine produced no significant difference in treatment completion, or severity of withdrawal, but withdrawal symptoms resolved more quickly.

Other detoxification agents and methods

Clonidine

The antihypertensive, α_2-adrenergic agonist drug clonidine has been used to facilitate opioid withdrawal in both inpatient and outpatient settings for over 25 years.[18-21] It works by binding to α_2 autoreceptors in the locus coeruleus and suppressing its hyperactivity during withdrawal. Doses of 0.4 to 1.2 mg/day or higher reduce many of the autonomic components of the opioid withdrawal syndrome, but symptoms such as insomnia, lethargy, muscle aches, and restlessness may not be adequately handled.[22]

Compared with methadone-aided withdrawal, clonidine has more side effects, especially hypotension, but is less likely to lead to post-withdrawal rebound. Dropouts are more likely to occur early with clonidine and later with methadone. In a study of heroin detoxification, buprenorphine did better on retention, heroin use, and withdrawal severity than the clonidine group.[12] Since clonidine has mild analgesic effects, added analgesia may not be needed during the withdrawal period for medical opioid addicts.

Lofexidine

Hypotensive effects may limit the optimal dosing of clonidine for opioid withdrawal. Lofexidine, an analogue of clonidine, has been approved in the UK and may be as

effective as clonidine for opioid withdrawal with less hypotension and sedation.[23,24] Combining lofexidine with low-dose naloxone appears to improve retention symptoms and time to relapse.[4,25-28]

Supportive measures

Insomnia is both common and debilitating. Clonazepam, trazodone, and zolpidem have all been used for withdrawal-related insomnia, but the decision to use a benzodiazepine needs to be made carefully, especially for outpatient detoxification.

Treatments for ancillary withdrawal symptoms include nonsteroidal anti-inflammatory drugs (eg, ibuprofen or ketorolac tromethamine) for muscle cramps or pain; bismuth subsalicylate for diarrhea; prochlorperazine or ondansetron for nausea and vomiting; and α_2-adrenergic agents (eg, clonidine) for flu-like symptoms. Vitamin and mineral supplements are often given.

Rapid detoxification methods

Clonidine-naltrexone detoxification

This method[29-31] combines a rapid, precipitated withdrawal by naltrexone producing severe withdrawal symptoms, with high doses of clonidine and benzodiazepines before and after the naltrexone to ameliorate the symptoms. While shortening withdrawal to 2 to 3 days, evidence is lacking of longer abstinence or naltrexone retention.[32]

Rapid opioid withdrawal under general anesthesia

To decrease further the time needed for withdrawal, a rapid detoxification procedure using general anesthesia was developed[33] and gradually improved.[34-37] A variety of medications have been used, including naltrexone or nalmefene, propofol anesthesia or heavy midazolam sedation, the antiemetic ondansetron, the antidiarrheal octreotide, and clonidine and benzodiazepines for other withdrawal symptoms, and has been carried out on either an inpatient or outpatient basis. Post-procedure therapy varies widely. Claims of high rates of abstinence months after detoxification have been made, but no objective verification exists, and the samples are not representative.[38] Significant withdrawal symptoms may persist for days or even weeks after the procedure in humans[15,39,40] or in rats,[41] and there appears to be no longer-term improved outcome at 1 to 3 months

later.[15,42,43] Internationally, over one dozen deaths have been reported, usually within 72 hours of the procedure, with pulmonary edema a common complication.[44-47]

Pregnancy

Illicit opioid use during pregnancy can have numerous harmful effects on the woman, fetus, and neonate. Residential abstinent treatment is usually not available. Methadone maintenance is thus the standard approach.[48] While the infant will be physically dependent on methadone and about half need to be withdrawn, no birth defects are associated with such exposure, if prenatal care is adequate. Withdrawal from methadone maintenance is usually not preferable, but if carried out it should occur during the second trimester at no greater than 5 mg/week. Methadone metabolism is increased during pregnancy, and plasma half-life decreased. The clinician must balance the risk of illicit opioid use if the dose is too low, and the risks of the neonatal abstinence syndrome (NAS) if the dose is too high. This can be somewhat ameliorated by split dosing. Studies of pregnant methadone-maintained women found decreased narcotic use and improved health and prenatal care. Fetal growth and perinatal outcomes also improved. These benefits diminish with continued use/abuse of licit (alcohol and tobacco) or illicit (cocaine and marijuana) substances.[49]

Maintenance on buprenorphine is a more recent development with published reports of over 300 pregnancies, with good fetal outcomes. Buprenorphine appears comparable to methadone on outcome measures as assessed by NAS and maternal and neonatal safety.[50-54] One study[52] reported shorter hospital stays for babies born to buprenorphine-maintained mothers in comparison to methadone. Long-term effects beyond the neonatal period, however, are not sufficiently studied.

Agonist maintenance: methadone

Pioneering work by Dole and Nyswander in the 1960s[55-57] provided the initial scientific basis for using the long-acting opioid agonist methadone for maintenance. Numerous studies since then[58-62] have demonstrated that methadone maintenance of opioid addicts substantially reduces mortality and morbidity, the risk of new human immunodeficiency virus (HIV) infection, criminal activity, and illicit opioid use, especially when used with enhanced ancillary services.[63] Unfortunately, many pro-

grams do not provide these services, both because of decreased government funding and increased private ownership. In the US, there are over 240 000 individuals maintained on methadone, while in some other countries, eg, Russia, government opposition to agonist maintenance prevents its use, even when high HIV rates exist.

Federal regulations

With a few exceptions, methadone may only be dispensed for opioid detoxification or maintenance treatment by opioid treatment programs certified by the Substance Abuse and Mental Health Administration (SAMHSA) and approved by the appropriate state agency. Depending on criteria such as continued illicit drug use and employment, an increasing number of take-home doses is permitted, up to a maximum of a 1-month supply after 2 years or longer.

Pharmacology

While heroin is short-acting and relatively ineffective orally, methadone is a long-acting, and orally effective, opioid. It is excreted primarily in the urine and is an agonist at μ and δ opiate receptors.

Methadone is primarily metabolized through cytochrome P450 (CYP) enzymes, predominantly involving the CYP3A4 pathway. Drugs that increase the P450 enzymes, such as the retroviral agents for treating HIV, may increase methadone metabolism and lead to withdrawal symptoms, even in stable maintained patients. In contrast, drugs that inhibit these enzymes, such as some selective serotonin reuptake inhibitor (SSRI) antidepressants, may increase methadone levels and sedation.[64-68] Effects are more likely early in treatment before plasma levels have stabilized.[69] Physicians using methadone are advised to consult tables of drug interactions for complete listings.

Dosing

Methadone's plasma half-life, once stabilized, averages 24 to 36 hours[70] with a range of 13 to 50 hours, making it a useful once-daily maintenance medication compared with morphine or heroin. However, up to 10 days may be needed for such a steady state and before that, new patients, either in maintenance or given methadone for analgesia, are at risk of fatal overdose.[8,71] Doses should not exceed 40 mg/day the first day of dosing or be

increased over the next 2 weeks by more than 5 to 10 mg every 2 to 3 days. Individual differences in rate of metabolism may produce complaints of withdrawal symptoms, even in those on a stable dose.

Doses of 30 to 40 mg of methadone prevent most withdrawal symptoms and craving, but are not high enough to block the reinforcing effects of high doses of potent heroin. Doses of greater than 80 mg/day are associated with fewer positive urine tests than 40 mg, and programs with average doses of 80 to 120 mg have consistently better results than those with lower average doses.[72-75] As heroin potency increased, the average daily dose of methadone doubled in the 1990s.[76] Some programs today dose as high as 350 mg/day using the rationale of individual metabolic differences. Such doses have at times been associated with increased street sales.

Safety

Studies of methadone maintenance have not found long-term damage to the heart, kidneys, liver, or lungs.[77-79] Further, long-acting maintenance medications normalize the neuroendocrine alterations induced by short-acting opioids and with minimal psychoactive impairment,[80] unless accompanied by high concomitant use of benzodiazepines and alcohol found in many methadone programs. The most common side effects of methadone maintenance are constipation, sweating, urinary retention, and dose-related orgasm dysfunction in men.

Methadone overdose has been a problem with accidental ingestion by children (10 mg has been a fatal dose), use by nondependent opioid users experimenting with methadone, or during initiation of maintenance. While rapid treatment of overdose with narcotic antagonists can lead to full recovery, it is important to keep such individuals under observation for at least 24 hours and follow the initial naloxone treatment with a long-acting antagonist such as nalmefene. Death may occur even 24 hours or more after the methadone intake. Other factors associated with increased risk of overdose include medications that inhibit CYP3A4, use of alcohol or benzodiazepines, or liver disease. The possibility of cardiac conduction defects with methadone, especially at doses higher than 120 mg/day,[81] led to a black-box warning for methadone in December 2006.

Driving by patients on long-term methadone maintenance has not been found to be impaired,[82] but patients should be warned about driving after using alcohol, illicit drugs, or sedating medications. As with patients withdrawing from alcohol, patients beginning methadone maintenance may have some short-term cognitive impairment early in treatment.[83]

Nonpharmacologic components

Methadone is a medication, not a treatment. To achieve its potential, methadone maintenance should be combined with counseling aimed at lifestyle change. A classic study[63] demonstrated this by randomly assigning patients to minimal counseling, standard drug counseling, or enhanced services while maintaining them on identical standard daily methadone doses. Patients in the minimal counseling group had substantially higher illicit cocaine and opioid use than the other 2 groups. By 12 weeks, 69% of the patients in the minimal counseling group had 8 consecutive weeks of illicit opiate or cocaine use or three emergency situations compared with 41% of those receiving standard counseling and 19% of those receiving enhanced services. Recently a number of behavioral approaches, eg, contingency contracting and voucher incentives, have also shown efficacy, especially if staff is appropriately trained.[84]

While appropriate therapy is better than no therapy, some randomized studies have suggested that methadone alone is better than being on a waiting list.[85,86] Such methadone maintenance is permitted for up to 120 days in areas with long waiting lists.

Co-occurring disorders

There is high prevalence of comorbid psychiatric and substance abuse disorders among opioid addicts, as well as diseases common because of drug lifestyle, eg, acquired immune deficiency syndrome (AIDS), hepatitis B or C, and tuberculosis.[87] Since treatments for HIV and hepatitis C can stabilize these disorders, methadone programs need to screen and refer patients for medical treatment, as well as providing or referring for psychiatric disorders if patients are to adequately recover.

Pain

Over one third of methadone maintenance patients are estimated to have moderate-to-severe chronic pain. They have become tolerant to methadone's analgesic properties and may even have increased pain sensitivity.[88]

Treating methadone-maintained patients for acute pain with opioid analgesics has not been found to lead to relapse or higher methadone doses post-treatment.[89] The regular, daily methadone dose should be continued, and analgesic medications including nonopioid analgesics or short-acting opioids added as clinically indicated.[90,91] Since methadone occupies less than one third of the μ opioid receptors, unoccupied receptors are available for analgesic response.[92] However, methadone-maintained patients might require higher doses or more frequent administration of opioid analgesics than nonmaintained patients.

Office-based methadone maintenance treatment

Office-based methadone maintenance has been permitted on a limited basis for patients who have been stable for at least a few years. In general, patients on this "medical maintenance" have been successful[93,94] but a number increased their use of illicit drugs.[95-98] While the number of patients on methadone maintenance has increased to 240 000, there remain many parts of the country with inadequate availability and long waiting lists.

Discontinuation of methadone maintenance

How long patients should remain on methadone maintenance is controversial. Those on methadone do better than those who stop, with relapse common in this latter group. Methadone maintenance's contributions to improved health and functioning may increase slowly over time, but markedly decreases when methadone is discontinued. The risk of relapse following withdrawal from methadone maintenance is high, even for patients who have been on it for long periods and have made substantial changes in lifestyle. In this era of AIDS, the risk of serious adverse consequences following relapse suggest that for many patients lifetime maintenance may be necessary.[99-101] There is substantial political opposition to methadone maintenance, which manifests itself in problems locating clinic sites, lack of economic support, and family opposition. The clinic–based nature of the programs, which mix stable patients and newly maintained patients, along with inadequate staffing, and minimal incentives for patient change, can lead to a culture of continued illicit drug use and chronic unemployment.[94] In spite of many decades of improving and saving lives, methadone maintenance is often viewed as perpetuating addiction or being immoral. The traditional method of withdrawal is decreasing the methadone dose rapidly until 30 mg is reached, and then slowly tapering from that, eg 5 mg/week or switching to clonidine.[102,103] A more recent approach involves transferring the patient to buprenorphine/naloxone and then tapering as described in the section on discontinuing buprenorphine.[103]

Partial agonist maintenance

Buprenorphine

Buprenorphine, a Schedule III controlled substance, is a high affinity partial μ-opioid agonist, κ antagonist, and ORL-1 receptor agonist.[104] Studies from 1980 on found it useful for treating opioid withdrawal and dependence.[105-109] Office-based buprenorphine maintenance has already increased treatment availability for opioid-dependent individuals and brought into treatment populations that had been unable or unwilling to attend methadone maintenance clinics, eg, prescription opioid addicts. Prescription opioid addicts seeking office-based buprenorphine are likely to present different issues than heroin addicts applying for methadone maintenance.[110] Primary-care physicians who have not treated opioid dependence will also present new challenges to the field. Anecdotal reports describe patients on buprenorphine as feeling more clear-headed, more energetic, and more aware of emotions than on methadone maintenance.[111] To diminish possible diversion to parenteral use, the recommended form of buprenorphine is a 4:1 combination with naloxone (Suboxone). The mono form (Subutex) is used for pregnant women and, at times, for induction.

Federal regulations

In 2002, the FDA approved buprenorphine for the treatment of opioid dependence in office-based practice. It was already being used for such treatment in other countries. Physicians need to receive 8 hours of specialized training in person or online, and then apply for a waiver from the Department of Health and Human Services. They are limited to 30 patients on buprenorphine for the first year, and can then apply to increase the number to 100.

Pharmacology

Buprenorphine binds to the μ receptor and activates it, but as the dose increases, there is a ceiling on some opi-

oid agonist effects, such as respiratory depression, making it safer than a full agonist as far as overdose. This has been demonstrated by the differential effects on overdose deaths in France of methadone and buprenorphine.[112] The ceiling effect is approximately 32 mg of sublingual buprenorphine, but it may be possible to increase analgesic effects above that.

Because buprenorphine is best absorbed parenterally and poorest orally,[113-115] with sublingual bioavailability in between, and naloxone is poorly absorbed orally but about 20 times more parenterally, the sublingual combination tablet yields primarily a buprenorphine effect. If crushed and injected, both drugs are bioavailable.[114,115] Naloxone will then precipitate opioid withdrawal if the individual is opioid-dependent, unless only on buprenorphine. Buprenorphine alone will also precipitate withdrawal by displacing other opiates from the receptor. Individuals who use *only* buprenorphine can get high even if they inject the combination product, but it is not as reinforcing.[116]

There have been a number of reports of buprenorphine abuse in some countries, including France,[117] Finland,[118] Great Britain,[119] and Australia.[120] Only Finland has, since 2004, the combination product. A recent study from Finland found a very high rate of buprenorphine intravenous (IV) use but 75% of such users said they were using it to self-medicate addiction or withdrawal. Over two thirds had tried the combination IV but 80% said they had a "bad experience." As a result, the street price of the combination was less than half of the mono product.[121]

Buprenorphine undergoes metabolism by the liver, primarily by the cytochrome P450 3A4 enzyme system[122,123] but studies have not found clinically significant interactions with HIV medications that interact with this system,[124] with the possible exception of atazanavir/retonavir.[125] Buprenorphine's terminal half-life of 37 hours and slow-onset and offset enables every-other-day dosing, although that tends not to be the preferred spacing by patients. Buprenorphine's high affinity at the μ receptor means it will block most opioid agonist effects,[126,127] but because of its ceiling effect, one can override the blockade by using higher agonist doses.[128,129]

Induction

For practical reasons, buprenorphine induction is usually done on an outpatient basis, with induction divided into two visits: initial evaluation for suitability, answering questions and giving instructions for the second visit; and actual induction. Induction may take 2 hours or longer, and patients should not drive that first day. When distance or other factors prevent two visits, careful telephone preparation is important.

Buprenorphine can displace a full opioid agonist from the μ receptor, but since it is only a partial agonist there could be precipitated opioid withdrawal. At induction, therefore, the addicted patient should be in withdrawal: off short-acting opioids for at least 12 to 16 hours and long-acting ones for at least 36 hours. When the patient is transferring from methadone maintenance, the program needs to verify the methadone dose as 40 mg or less and history of compliance with rules, especially drug use.

While 4 mg of buprenorphine is often used as the initial dose,[103] if there is doubt about the patient's withdrawal symptoms, the buprenorphine dose should be lowered to 2 mg. If the initial dose of 2 or 4 mg is tolerated, a similar second dose can be given an hour later and then 4 mg 6 to 8 hours later. The total dose on day 1 usually should not exceed 8 to 12 mg. If any dose *worsens* withdrawal symptoms, the buprenorphine should be temporarily halted and the symptoms treated with oral clonidine 0.1-0.2 mg. Once symptoms have improved, the buprenorphine can be restarted. *It is better to err on the side of incomplete suppression of withdrawal on day 1 than to have precipitated withdrawal, which may drive the patient away.*

By day 2 or 3, a dose of 12 to 16 mg is usually reached and resolves most withdrawal symptoms. Clonidine can be used to treat residual mild symptoms for a few days to a week as long as the patient does not become hypotensive. The most difficult and distressing symptom is usually insomnia. Depending whether there is a history of benzodiazepine abuse, agents chosen to treat this include trazodone, zolpidem, or clonazepam.

The usual maintenance dose is 16 to 24 mg/day although some patients are comfortable at 8 to 12 mg and others need 24 to 32 mg. Many patients prefer taking the buprenorphine in divided doses, two or three times a day, as opposed to only once.

Patient selection issues

The patient first needs to meet the criteria for opioid dependence. Abuse of, or dependence on, other sub-

stances such as alcohol, benzodiazepines, and cocaine, along with need for sedative detoxification, history of previous treatments, and psychiatric problems should all be explored.

Detoxification or maintenance

Many patients initially request buprenorphine detoxification and then change their minds a few weeks later and request maintenance. Given the high relapse rate post-withdrawal, this request may be reasonable. However, buprenorphine is relatively easy to detoxify *with* but harder to detoxify *from*. Thus, withdrawal should not be stretched out longer than 2 to 3 weeks if maintenance is not the ultimate goal.

Maintenance on buprenorphine vs methadone

If the patient's lifestyle is unstable, eg, homelessness, or needs the structure of regular attendance in a dispensing situation, or needs the wider range of services available in a comprehensive methadone maintenance program, or lacks the insurance or financial wherewithal to pay for buprenorphine medication and therapy, the patient may be better served by a methadone maintenance program. Since buprenorphine is a partial μ agonist with maximal efficacy approximately equal to 70 mg of methadone, it may not be adequate for some patients. Optimal methadone doses average around 100 mg/day and some patients require much higher doses.[129] A meta-analysis[130] found that both methadone and buprenorphine maintenance could be equally effective, but there was a wide variation in the studies covered. A way around this dilemma is to use a stepped approach whereby patients would be started on buprenorphine and increased as necessary up to 32 mg/day. If clinical results are inadequate, the patient would be moved to methadone maintenance and dosed as needed.[131] For patients who clearly need the structure of a methadone program, but prefer buprenorphine, it could be dispensed by a methadone program using the same rules as methadone.

Use of buprenorphine vs the buprenorphine/naloxone combination

It is preferable to maintain patients on the combination product unless they are pregnant or trying to become so. Many clinicians prefer the mono form for the initial induc-

tion, either because of concern for possible pregnancy or so that they do not need to worry about whether unrelieved withdrawal symptoms are due to increased amounts of naloxone being absorbed. The patient should be switched to the combination form once stable.

Age

While buprenorphine withdrawal or maintenance is legal above the age of 16, short-term dependence may be better handled by withdrawal and intensive counseling.

Other laboratory tests

In addition to testing for drugs of abuse, patients should be evaluated at baseline by the usual medical screening tests, as well as pregnancy, when appropriate, and tests for hepatitis B, C, HIV, and tuberculosis. Baseline tests can be carried out by the patient's own physician or ordered by the prescribing doctor.

Use of other drugs

The safety of buprenorphine on respiratory depression can be thwarted by concomitant use of benzodiazepines or other sedatives, especially when both the buprenorphine and the benzodiazepines are injected. A number of deaths have been reported from France due to this.[112,132] Low-dose oral benzodiazepines used judiciously do not appear to present the same problem.

The effect of buprenorphine maintenance on cocaine use in opiate addicts remains unclear. Some clinical studies have demonstrated efficacy in reducing cocaine use[133,134] while others have been inconclusive[135] or negative.[136]

Maintenance

Counseling

Buprenorphine and methadone are medications, not treatments, and should be combined with appropriate counseling services. The prescriber does not have to provide the counseling but convenient access will enhance compliance. Counseling can be individual, group or family therapy, or combinations. However, therapists have reported that many patients feel so well on buprenorphine compared with either methadone or their previous illicit drug use that they resist counseling.[111]

Urine testing

Drug testing, via "dipsticks" or commercial laboratories, can detect use of illicit opioids, cocaine, or benzodiazepines. The testing strips are easily used in the office but the standard opiate strips usually do not test for buprenorphine, methadone, hydrocodone, or oxycodone, so specific tests for these drugs are necessary to avoid false-negative results.[103] The test frequency and whether it is scheduled or random is a function of the physician's judgment in each case.

Maintenance

Once symptoms of opiate withdrawal and use of other opioids has been significantly decreased or eliminated, the maintenance phase begins. Dose increases may occur either because the patient is continuing illicit opioid use while apparently complying with the buprenorphine (monitored dosing may be necessary), or because the patient complains that the dose is not sufficient. Changing the frequency or scheduling of the buprenorphine doses may improve the latter. Although buprenorphine has a long half-life, some patients report better results by dosing 3 times/day, eg, 8 mg AM, PM, and late evening. The final dose is usually 8 to 24 mg/day[103] but some patients appear to need 32 mg. If illicit opioid use continues in spite of high buprenorphine doses and therapy, referral for methadone maintenance or depot naltrexone may be necessary. Before that final step, it may be worthwhile to try contingency contracting using frequency of visits or weeks prescribed as the reward.[137] Psychiatric problems can be common (over 50% in one unsolicited sample).[138] Appropriate medications or other approaches might markedly reduce the illicit drug use and make transferring unnecessary. Office visits once a week are usually recommended initially[103] and can be reduced if the dose is stable, illicit drug use has stopped, and more intense psychological intervention is not needed. However, there may be practical obstacles to this, such as distance from the physician or problems paying for the medication and doctor's visit if not adequately covered by insurance. Frequency can be reduced gradually with stable patients to once monthly.

Side effects

Buprenorphine does not appear to cause liver abnormalities but, as with other narcotics, side effects such as constipation, nausea, and decreased sexual interest have been reported.[139] Unlike methadone, buprenorphine maintenance does not appear to be associated with electrocardiographic abnormalities.[140] Buprenorphine's desirable mood effects compared with methadone[111] may relate to methadone's producing a significant opioid effect lasting from 2 to 5 hours after dosing in maintained patients.[141,142] This may interfere with everyday activities.

Other issues

Acute pain

Acute pain is more difficult to manage with buprenorphine compared with a full agonist, but there are a number of options. These include dividing the daily buprenorphine dose into 3 or 4 doses and adding nonopioid analgesics; adding a full μ opioid analgesic on top of the buprenorphine dose; switching the patient temporarily over to a short-acting full μ agonist and increasing the dose until adequate pain relief occurs; or using nonopioid ways of dealing with pain such as regional or general anesthesia in a hospital setting.[90,91,143]

Chronic pain

Many patients with chronic pain can be treated with buprenorphine doses of 24 to 32 mg divided into 3 or 4 daily doses and supplemented if necessary by nonopioid analgesics. If pain relief is not sufficient, or the patient is resorting to illicit opioid use to control it, transfer to methadone maintenance may be needed.

Discontinuation of buprenorphine maintenance

While there is no legal limit to the length of buprenorphine maintenance, many patients ask to be withdrawn a few months after being maintained. The usual reasons are desire to be off all narcotics or the cost. Patients often have an unrealistic expectation of how easy it will be to remain abstinent[144,145] and many (perhaps most) will relapse within a short period.

Patients should be encouraged to remain on maintenance and, when possible, alternative solutions sought for issues like cost, eg, reducing frequency of visits, or exploring insurance options. There is no adequate data on the optimal length of time; each patient must be judged indi-

vidually using issues such as previous relapses, addiction history, and lifestyle stability. It is not uncommon to need a number of episodes of opioid maintenance or even long-term maintenance.

There is no consensus on the best way to withdraw from buprenorphine maintenance other than to do it gradually, eg, 2 mg/week until 4 mg is reached and then 1 mg decreased every other week or monthly. Clonidine may be useful in the final weeks to deal with the withdrawal symptoms. Relapse back to illicit opioid use should be taken seriously and the dose raised until the use stops. Continued use should probably be handled by resuming full-scale maintenance. As yet, there are no adequate controlled studies comparing the ease or severity of withdrawal from maintained buprenorphine vs methadone patients, although earlier studies suggested that buprenorphine withdrawal might be better tolerated.[146,147] Once the patient has completed detoxification, use of naltrexone for at least 3 months may help prevent relapse. The 1-month depot naltrexone is preferable, but may be too expensive unless covered by insurance.

Naltrexone

Naltrexone was approved by the FDA as an opioid antagonist in 1984. It is effective orally and is long-acting, depending upon dose. While methadone blocks heroin effects by cross-tolerance, naltrexone blocks the effects by competitive antagonism at the μ receptor. The degree of blockade is a function of the concentrations of agonist to antagonist, and their receptor affinity.

Because of the blocking action of naltrexone, self-administration of opioids at usual doses produces no euphoria so that either individuals cease heroin use or cease taking the naltrexone.[148] Its long duration of action means that naltrexone can be given two or three times per week, but daily administration is usually preferred, both because of developing a regular habit of use and of creating a higher blockade. Less frequent administration is usually employed when an individual is taking monitored doses. Tolerance does not develop to the opioid antagonism, even after almost 2 years of regular use.[149] The FDA approved a 1-month acting depot preparation of naltrexone in 2006 for the treatment of alcoholism,[150] but it can be used off-label for treatment of opioid dependence.[151]

Dropout rates with naltrexone are high, but are significantly better where there is substantial external motivation, such as in physicians whose performance is being impaired, those involved with the criminal justice system, and those facing loss of an important job.[152-156] Retention is also better (43% at 6 months) in Russia, where addicts are often young adults living with parents who monitor intake and no agonist maintenance is permitted.[157]

Clinical aspects

If naltrexone is given to an opioid-dependent individual, it displaces the drugs from the receptor, producing rapid, unpleasant withdrawal. To avoid this, 5 to 7 days after the last use of a short-acting opioid or 7 to 10 days after the last dose of methadone is necessary before naltrexone induction. Using one of the rapid withdrawal methods described earlier can shorten the waiting period. Mild symptoms of precipitated withdrawal can usually be treated with clonidine and clonazepam. If sufficient abstinence is unclear, a test dose of a small amount of IM naloxone (eg, 0.2 mg) can be used.[157,159] Any withdrawal produced will be short-lived. Naltrexone should be initiated with a dose of 25 mg and, if that produces no withdrawal, the second 25-mg dose can be given 1 hour later. If depot naltrexone is to be used, it is useful to have 1 to 2 days of a well-tolerated 50 mg oral dose.

For oral naltrexone, virtually 100% adherence is needed because the blockade wears off around 24 to 48 hours after the last dose. Missed doses often eventuate in relapse, after which another detoxification and naltrexone induction is needed. Behavioral treatments have been found to be helpful in improving naltrexone adherence and treatment retention, doubling retention rates at 12 to 24 weeks. Approaches have included voucher incentives contingent on pill-taking adherence and involvement of family in monitoring such adherence.[160-165]

When possible, all doses should be monitored either by a family member or a health professional. Three times per week dosing (100 mg, 100 mg, 150 mg) may be useful if daily monitoring is difficult to arrange. Individuals doing monitoring should be trained to look for "cheeking" and other ways to avoid ingestion. Involvement in self-help groups such as Alcoholics Anonymous or (AA) or Narcotics anonymous (NA) should be encouraged. While such groups usually oppose agonist maintenance, naltrexone is often tolerated because of its lack of psychoactive effects. Urine tests should be carried out, if possible on a random basis, to see if the individual is using opioids, suggesting missing naltrexone doses, or has switched to drugs such as cocaine or benzodiazepines.

Side effects

Nausea, headache, and dysphoria have been reported, especially during the first 4 weeks of naltrexone administration. These symptoms resemble mild protracted opioid withdrawal and usually go away on their own or can be ameliorated by clonidine. Elevated liver enzymes, especially transaminases, were noted decades ago in patients given high doses (eg, 300 mg/day) as experimental obesity treatment. They reversed when the drug was halted, as they have when occasionally observed in patients taking normal doses.[166] If the enzymes are not reduced, brief hospitalization to stop excess alcohol intake or tests for such excessive drinking can be diagnostic.[167,168] Patients should be evaluated for viral hepatitis, which is very common among former IV users. Because of the possibility of hepatic effects, baseline liver function tests should be carried out. If abnormal (greater than 3 to 5 times normal), naltrexone should not be started. Monthly lab retests for the first 3 months can be a useful precaution.

Although naltrexone affects a variety of endocrine functions,[169-172] such effects have not been associated with particular problems. Likewise, although upregulation of opioid receptors has been reported in rodents, it was not found in a human study. Thus, the main risk of heroin overdose post naltrexone appears to be from loss of tolerance.[148]

Treatment of pain

When patients on naltrexone need analgesia, such as after surgery or in emergency situations, nonsteroidal anti-inflammatory drugs (NSAIDs, eg, Ketorolac) should be tried. If not adequate, the blockade can be surmounted by large doses of full agonists but this should only be done in an environment where emergency ventilation is available as in a hospital or emergency room because of the danger of overdose.

Duration of maintenance

There are no clear guidelines on the duration of naltrexone maintenance although, in general, 6 to 12 months are probably a minimum depending on the circumstances. Careful clinical evaluation of relapse risk should be done prior to the decision to discontinue naltrexone. The 30-day depot injection may improve compliance. Because naltrexone is an antagonist, it can be stopped abruptly without withdrawal symptoms. The high dropout rates and patient preference for agonist treatments will probably continue to keep antagonists in a secondary role and in select populations unless agonist maintenance is not available.[173,174]

Conclusion

Compared with other drugs of abuse, opioid dependence benefits from a wider range of available pharmacological tools for treatment. In spite of this, the large majority of the 1 million heroin addicts and 2 to 3 million prescription opioid abusers are not receiving treatment, and those who enter often only seek detoxification, from which early relapse is the most common outcome. The most successful treatment is long-term maintenance on agonists such as methadone and buprenorphine, but a variety of obstacles, including government regulations, cost, availability, and stigma, combine to diminish their use. The death rate among heroin addicts is approximately 2% to 3% per year, significantly higher than among their age- and socioeconomically matched cohorts. In addition to dealing with the obstacles above, what is needed to decrease this are new approaches that deal with the brain changes produced by chronic dependence and could reverse the intracellular changes related to addiction and craving. ❏

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Pharmacological aspects

Tratamientos farmacológicos para la dependencia de opioides: opciones para la detoxificación y el mantenimiento

Aun cuando la dependencia de opioides tiene más agentes terapéuticos disponibles que otras drogas de abuso, ninguno de ellos resulta curativo. Sin embargo, estos agentes pueden disminuir marcadamente los síntomas de abstinencia y el craving, y bloquear los efectos de los opioides debidos a las recaídas. El método más efectivo para tratar la abstinencia es la sustitución y disminución progresiva con metadona o buprenorfina. Los agentes alfa-2 adrenérgicos pueden reducir los síntomas no tratados o reemplazar a los agonistas si no se dispone de ellos. Se ha estudiado la reducción del período de abstinencia utilizando antagonistas narcóticos, pero los temas de seguridad o de la persistencia de síntomas han dificultado su desarrollo. La mejor evolución a largo plazo no se relaciona ni con los métodos ni con los agentes usados para manejar la abstinencia, sino que se asocia con el tratamiento post-detoxificación. Excluyendo a aquellos pacientes que cambian de hábito en el corto plazo, la mejor evolución ocurre cuando se mantiene metadona o buprenorfina a largo plazo, junto con adecuadas intervenciones psicosociales. En aquellos pacientes con una fuerte motivación externa puede ser útil el uso del antagonista naltrexona. Actualmente no hay claridad respecto a la duración de los tratamientos de mantenimiento. Se requiere de mejores agentes para combatir los cambios cerebrales relacionados con la adicción.

Traitements pharmacologiques de la dépendance aux opioïdes : détoxification et traitement d'entretien

Les traitements de la dépendance aux opioïdes, bien que plus nombreux que ceux des autres substances addictogènes, ne sont pas curatifs. Ils peuvent néanmoins diminuer notablement les symptômes de sevrage et la compulsion de consommation et bloquer les effets opioïdes dus aux récidives.
La méthode de sevrage la plus efficace est celle de la substitution et de la réduction progressive par la méthadone et la buprénorphine. Les agents α-2 adrénergiques peuvent améliorer les symptômes non traités ou remplacer les agonistes s'ils ne sont pas disponibles. On a cherché à raccourcir la période de sevrage en la déclenchant par des antagonistes narcotiques mais des problèmes de tolérance ou de persistance des symptômes en ont gêné le déroulement. L'amélioration à long terme n'est liée ni aux produits de sevrage ni aux méthodes mais plutôt au traitement qui suit la détoxification.
En excluant les produits avec lesquels l'accoutumance survient à court terme , les meilleurs résultats sont obtenus avec le maintien au long cours de la méthadone ou de la buprénorphine accompagné d'interventions psychosociales adaptées. Les patients dont la motivation externe est forte pourront préférer l'antagoniste naltrexone. Actuellement, la durée optimale de maintien de l'un ou de l'autre n'est pas bien définie. De meilleurs produits sont attendus pour traiter les modifications cérébrales liées à la dépendance.

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