

Clinical Detoxification Protocols

Some detoxification procedures are specific to particular drugs of dependence; others are based on general principles of treatment and are not drug specific. In this chapter, the general principles are presented first, followed by specific treatment regimens for each category.

Principles of Detoxification

- **Detoxification *alone* is rarely adequate treatment for alcohol and other drug (AOD) dependencies.** The provision of detoxification services without followup to an appropriate level of care is less than optimum use of limited resources. The appropriate level of care following detoxification must be a clinical decision based on the individual needs of the patient.
- **When using medication regimens or other detoxification procedures, only protocols of established safety and efficacy should be used in routine clinical practice.**
- **Providers must advise patients when procedures are used that have not been established as safe and effective.** Such procedures are considered investigatory and should be carried out under an approved research protocol.
- **During detoxification, providers should control patients' access to medication to the greatest extent possible.** Patients who are AOD dependent generally cannot be relied on to take their medication as prescribed. Overdose with either the prescribed medication or other drugs is always a possibility. Because of this, treatment staff should administer as many of the patient's detoxification medications as possible. When it is not possible for the treatment staff to do so, another responsible person should assist the patient in taking the prescribed detoxification medication.
- **Initiation of withdrawal should be individualized.** Many persons come to treatment during times of personal crisis. To initiate withdrawal immediately may intensify their distress. In some cases, treatment staff may prefer to stabilize the patient on medication (for example, a patient using heroin may be stabilized on methadone) to resolve the immediate crisis before initiating withdrawal.
- **Whenever possible, clinicians should substitute a long-acting medication for short-acting drugs of addiction.** For example, when detoxifying a patient from alcohol, clinicians usually prescribe a slowly metabolized benzodiazepine such as diazepam (Valium) or chlordiazepoxide (Librium). This type of medication provides a gradual decline in blood level and a more controlled reversal of neuroadaptation.
- **The intensity of withdrawal cannot always be predicted accurately.** To assign patients to the appropriate level of care, it would be desirable to have empirically validated predictors of withdrawal severity. Unfortunately, no validated objective measures exist that would enable providers to predict with confidence a particular patient's intensity of withdrawal symptoms. Clinical

guidelines used to assess probable withdrawal severity include the amount and duration of patients' AOD use, the severity of their prior withdrawals (if any), and the presence of medical or psychiatric comorbidity. Clinicians should take into account the patient's medical history but should also be aware that it cannot be considered totally reliable.

- **Every means possible should be used to ameliorate the patient's signs and symptoms of AOD withdrawal.** Medication should not be the only component of treatment. Psychological support is extremely important in reducing patients' distress during detoxification. Also, to the extent that it is medically safe, patients should be physically active.
- **Patients should begin participating as soon as possible in followup support therapy such as peer group therapy, family therapy, individual counseling or therapy, 12-step recovery meetings, and AOD recovery educational programs.** Such services provide much-needed emotional support and provide alternative methods of coping with stresses that trigger AOD abuse. They provide general information about AOD dependence and goals for recovery. Overall health also can be addressed. Counseling on sexual health may include information on sexually transmitted diseases, human immunodeficiency virus (HIV) testing and education, and guidance on safer sexual practices. For injecting drug users, a drug-recovery educational program might include a discussion of the Centers for Disease Control and Prevention recommendations on needle exchange and disinfection.

Alcohol Detoxification

Most alcohol-dependent individuals can be detoxified in a modified medical setting, provided assessment is comprehensive, medical backup is available, and staff know when to obtain a medical consultation. As Gerstein and Harwood (1990) write,

Detoxification episodes are often hospital based and may begin with emergency treatment of an overdose. Much drug detoxification (an estimated 100,000 admissions annually) is now taking place in hospital beds. It is doubtful whether hospitalization (especially beyond a day or two) is necessary in most cases, except for the special problems of addicted neonates, severe sedative-hypnotic dependence, or concurrent medical or severe psychiatric problems. For clients with a documented history of complications or flight from detoxification, residential detoxification may be indicated. Detoxification may . . . be undertaken successfully in most cases on a nonhospital residential, partial day care, or ambulatory basis.

Patients who score higher than 20 on the Clinical Institute Withdrawal Assessment (CIWA-Ar) instrument should be admitted to a hospital.

Most patients can be detoxified from alcohol in 3 to 5 days. Providers should consider the withdrawal time frame in terms of when the patient will need the most support; for alcoholics, this occurs the second day after the last ingestion. Other factors that influence the length of the detoxification period include the severity of the dependency and the patient's overall health status. Patients who are medically debilitated should detoxify more slowly.

Assessing Alcohol Withdrawal Symptoms

The signs and symptoms of acute alcohol abstinence syndrome generally begin 6 to 24 hours after the patient takes his or her last drink. The acute phase of alcohol abstinence syndrome may begin when the patient still has significant blood alcohol concentrations.

Signs and symptoms may include

- Restlessness, irritability, anxiety, agitation
- Anorexia, nausea, vomiting
- Tremor, elevated heart rate, increased blood pressure
- Insomnia, intense dreaming, nightmares
- Impaired concentration, memory, and judgment
- Increased sensitivity to sounds, alteration in tactile sensations
- Delirium (disorientation to time, place, situation)
- Hallucinations (auditory, visual, or tactile)
- Delusions (usually paranoid)
- Grand mal seizures
- Elevated temperature.

Symptoms do not always progress from mild to severe in a predictable fashion. In some patients, a grand mal seizure may be the first manifestation of acute alcohol abstinence syndrome.

Although many programs devise their own methods of monitoring patients' withdrawal signs and symptoms, there is considerable advantage to using a widely accepted validated instrument. The CIWA-Ar is commonly used in clinical and research settings for initial assessment and ongoing monitoring of alcohol withdrawal symptoms. It "takes 2 to 5 minutes to administer, helps make the decision to hospitalize the patient or to treat him or her as an outpatient, and is useful for monitoring and managing the patient during withdrawal" (Fuller and Gordis, 1994). It measures the severity of alcohol withdrawal by rating 10 signs and symptoms: nausea; tremor; autonomic hyperactivity; anxiety; agitation; tactile, visual, and auditory disturbances; headache; and disorientation. The maximum score is 67 (Saitz et al., 1994). The CIWA-Ar is not copyrighted, and may be used freely.

The CIWA-Ar should be repeated at regular intervals (initially every 1 or 2 hours) to monitor patients' progress (Sullivan et al., 1989). Increasing scores on the CIWA-Ar signify the need for additional medication or a higher level of treatment; decreasing scores suggest therapeutic response to medication or treatment milieu. Patients scoring less than 10 on the CIWA-Ar do not usually need additional medication for withdrawal (Saitz et al., 1994.; Sullivan et al., 1989).

Benzodiazepine Treatment of Alcohol Withdrawal

Benzodiazepines, such as chlordiazepoxide (Librium), clonazepam (Klonopin), chlorazepate (Tranxene), and diazepam (Valium), are considered effective tools in ameliorating signs and symptoms of alcohol withdrawal because they decrease the likelihood and number of withdrawal seizures and episodes of delirium tremens. Chlordiazepoxide is "currently the most commonly administered medication for alcohol withdrawal in the United States" (Saitz et al., 1994). Oxazepam (Serax) or lorazepam (Ativan) are sometimes used with patients who have severe liver disease because neither is metabolized by the liver.

There are several acceptable medication regimens for treating alcohol withdrawal:

- **Gradual, tapering doses.** Oral benzodiazepines are administered on a predetermined dosing schedule for several days and gradually discontinued. This regimen is the one most commonly used. Dosing protocols vary widely among treatment facilities. As an example, patients may receive 50 mg of chlordiazepoxide (or 10 mg of diazepam) every 6 hours during the first day and 25 mg (or 5 mg of diazepam) every 6 hours on the second and third days (Saitz et al., 1994). Doses of withdrawal medication are usually omitted if the patient is sleeping soundly or showing signs of oversedation.

- **Symptom-triggered therapy.** Using the CIWA-Ar, nurses are trained to recognize signs and symptoms of alcohol withdrawal and to give a benzodiazepine to their patients only when signs and symptoms of alcohol withdrawal appear. Studies have demonstrated that appropriate training of nurses in the application of the CIWA-Ar dramatically reduces the number of patients who receive symptom-triggered medication (from 75 percent to 13 percent) (Wartenberg et al., 1990).
- **Loading dose.** Staff administer a slowly metabolized benzodiazepine for only the first day of treatment (Sellers et al., 1983). Patients in moderate-to-severe withdrawal receive 20 mg of diazepam (or 100 mg of chlordiazepoxide) every 1 to 2 hours until they show significant clinical improvement (such as a CIWA-Ar score of 10 or less) or become sedated. A 1985 study by Devenyi indicates that "oral diazepam loading alone may be sufficient to prevent withdrawal seizures in patients who have had them previously and who have no other reason for having seizures." A randomized, double-blind controlled study conducted in an inpatient Veterans Administration hospital and reported in 1994 (Saitz et al.) compared fixed-dose and symptom-triggered therapy and found that patients "treated with symptom-triggered therapy completed their treatment courses sooner and required less medication than patients treated using the standard fixed-schedule approach." Specifically, they received less chlordiazepoxide (median 100 mg versus 425 mg) and received treatment for a shorter period of time (9 hours versus 68 hours). This indicates that symptom-triggered therapy is an approach that could individualize and improve the management of alcohol withdrawal. "Future studies should evaluate the effect of symptom-triggered therapy on the cost and duration of hospitalization for treatment of alcohol withdrawal and should identify the patient populations for whom symptom-triggered therapy is most effective" (Saitz et al., 1994).

Some patients can be withdrawn from alcohol without medication treatment; however, guidelines for identifying patients who can safely be treated without medication have not been validated in controlled clinical trials. Clinically, it is safer to provide treatment for patients who may not need it than to withhold medication until patients develop severe withdrawal signs and symptoms.

Signs and symptoms of the acute phase of alcohol abstinence syndrome may include:

Restlessness, irritability, anxiety, agitation
Anorexia, nausea, vomiting
Tremor, elevated heart rate, increased blood pressure
Insomnia, intense dreaming, nightmares
Impaired concentration, memory, and judgment
Increased sensitivity to sounds, alteration in tactile sensations
Delirium (disorientation to time, place, situation)
Hallucinations (auditory, visual, or tactile)
Delusions (usually paranoid)
Grand mal seizures
Elevated temperature.

Other Medications

Carbamazepine (Tegretol)

Carbamazepine, a medication used for treatment of seizures, has been reported as effective in treatment of alcohol withdrawal. A controlled study comparing carbamazepine 800 mg/day to oxazepam 120 mg/day for treatment of alcohol withdrawal found that the two drugs precipitated equivalent scores on the CIWA-Ar. The study's authors concluded that "anticonvulsants with anticonvulsant properties may be superior to traditional benzodiazepines in preventing alcohol withdrawal seizures and in potentially reducing long-term neurologic, behavioral, and psychiatric complications of alcoholism. To our knowledge, no double-blind, controlled studies have directly compared carbamazepine to a benzodiazepine in the treatment of alcohol withdrawal" (Malcolm et al., 1989).

Propranolol (Inderal) and Other Beta-Blockers

Some of the autonomic nervous system hyperactivity of alcohol withdrawal (such as rapid heartbeat, elevation of blood pressure, sweating, and tremors) is ameliorated by medications, such as propranolol (Inderal) and atenolol (Tenormin), that block beta adrenergic receptors. Although effective in decreasing autonomic symptoms, beta-blockers do not prevent hallucinations and confusion or withdrawal seizures. Propranolol may increase the risk of delirium and hallucinations during alcohol withdrawal (Jacob et al., 1983).

Treatment of Delirium and Seizures

Delirium tremens and seizures are two severe physiologic responses to withdrawal from sedative-hypnotics. Patients who develop delirium tremens with auditory, visual, or tactile hallucinations may need antipsychotic medications to ameliorate their hallucinations and to decrease agitation. Haloperidol, known by the trade name of Haldol, generally controls symptoms (0.5 to 2.0 mg every 4 hours by mouth or by intramuscular injection). Patients who are not vomiting may be given the medication by mouth; those who are severely agitated or vomiting may be administered Haldol intramuscularly. Patients should continue to receive benzodiazepines. Phenothiazines such as chlorpromazine (Thorazine) should not be used because of the increased risk of seizures.

Magnesium Sulfate

A controlled study has shown that magnesium sulfate does not reduce seizure frequency, even in patients with low serum magnesium levels (Wilson and Vulcano, 1984). More recent studies have affirmed the use of benzodiazepines to treat delirium tremens and seizures (Gorelick, 1993).

Phenytoin (Dilantin)

The therapeutic or prophylactic value of a routine prescription of phenytoin to prevent alcohol withdrawal seizures is not established (American Society of Addiction Medicine, 1994). The current consensus is that phenytoin or other anticonvulsant therapy appropriate for the seizure type should be used for patients with an established history of seizure disorder (seizures not caused solely by alcohol withdrawal). Expert opinion is mixed as to whether phenytoin (or other anticonvulsants) should be used in addition to adequate sedative-hypnotic medication in patients who are at an increased risk of alcohol withdrawal seizures because of previous withdrawal seizures, head injury, meningitis, encephalitis, or a family history of seizure disorder. Intravenous phenytoin is not beneficial for patients with isolated acute alcohol withdrawal seizures, but it may be indicated for patients who have multiple alcohol withdrawal seizures. Metabolism of phenytoin varies from patient to patient. It should be administered orally or intravenously because it is poorly absorbed when administered intramuscularly.

Phenobarbital

Phenobarbital can be used for alcohol detoxification when the patient is physically dependent on both sedative-hypnotics and alcohol.

Naltrexone

Naltrexone has been approved by the Food and Drug Administration (FDA) as a treatment adjunct to reduce relapse to alcohol dependence among detoxified alcohol-dependent patients. Naltrexone, previously marketed under the trade name of Trexan, is now marketed under the trade name of ReVia. The name change was made to prevent possible confusion with the benzodiazepine Tranxene.

Naltrexone is an opioid antagonist that has previously been used primarily to block the effects of heroin and thereby reduce the likelihood of relapse. Its mechanism of action in reducing alcohol consumption is not understood; however, clinical trials support its efficacy when it is used in conjunction with training in coping skills and/or supportive therapy (O'Malley et al., 1992; Volpicelli et al., 1992). It appears to reduce alcohol craving and thus is associated with less frequent and shorter relapses.

The National Institute on Alcohol Abuse and Alcoholism cautions that naltrexone should be administered only by doctors with knowledge of addiction treatment and as part of a structured treatment program. Researchers are still determining which populations are likely to respond best to naltrexone, and possible long-term side effects are under investigation.

Vitamins

Alcohol-dependent patients may have vitamin deficiencies, particularly of thiamine. Patients should receive thiamine in addition to high-potency multivitamins.

Special Problems with Medication Administration

Patients in alcohol withdrawal who are vomiting or who are in acute delirium may not be able to take oral medications. The absorption of diazepam or chlordiazepoxide after intramuscular administration is unpredictable. Intramuscular absorption of lorazepam (Ativan) is more reliable than that of diazepam or chlordiazepoxide. Lorazepam may be administered in doses of 2 mg every hour until signs and symptoms subside.

Outpatient Treatment Concerns

Increasingly, providers and patients are choosing the option of outpatient detoxification in part because of cost and in part because hospitalization (for other than serious sedative dependence) is considered unnecessary in most cases when there are no concurrent medical or severe psychiatric problems (Gerstein and Harwood, 1990). Providers must take into account some additional considerations when designing treatment plans for outpatients:

- Patients may have ready access to AODs at home.

- Patients may continue to use alcohol in addition to the prescribed detoxification medications. If they develop withdrawal symptoms, they may self-medicate with AODs. The combination of detoxification medications and other drugs may result in an overdose.
- Patients may have difficulty getting from their homes to their programs each day.
- Patients who are undergoing detoxification may experience side effects of withdrawal or breakthrough withdrawal.

Medical Complications of Alcohol Withdrawal

Fluid and Electrolyte Imbalances

Maintaining the patient's fluid and electrolyte balance is of key importance during detoxification. Most patients can be given fluids orally, beginning with juices and progressing to other liquids, such as soups. Solid foods should be added to the patient's diet only after he or she can tolerate liquids. Patients who are vomiting or having severe diarrhea should first be treated with sips of liquids that contain electrolytes. The amount can be increased to patient tolerance. Patients who become dehydrated should receive intravenous fluids containing electrolytes, dextrose, and thiamine (100 mg/bottle).

Patients withdrawing from alcohol are not always dehydrated; in fact, many are overhydrated. Parenteral fluid therapy may be harmful in these cases. During detoxification from alcohol, patients generally tolerate a mild degree of dehydration better than they do overhydration.

Hypoglycemia

Hypoglycemia is a significant danger during detoxification. Oral fluids should contain carbohydrates; orange juice may be one option. Parenteral fluids should contain 5 percent dextrose.

Fever

Any elevation of temperature in an individual who is undergoing withdrawal should be investigated. If the elevated temperature is a result of withdrawal, there is a need for additional medication and reevaluation of the detoxification schedule. If a patient has no other signs or symptoms of withdrawal, the elevated temperature is probably caused by an infection, and early aggressive antibiotic therapy may be necessary.

Psychiatric Comorbidity

While medical concerns must be addressed first via detoxification, any underlying psychiatric disorders must be dealt with as well. Failure to do so increases the risk of relapse. How to evaluate psychiatric conditions depends on the drug of abuse and the clinical situation. Because it is often difficult to differentiate between the symptoms of AOD abuse and those of various psychiatric conditions that may exist, it is preferable to do a thorough psychiatric work-up after a patient has withdrawn from the drug of abuse. This may not always be possible.

Suicidal patients can be detoxified, but they should be placed in an acute inpatient psychiatric setting rather than in an outpatient detoxification setting. These patients require close supervision by medical staff who understand both psychiatric and detoxification issues. The individual who takes the patient's history should include questions about suicidal feelings and previous suicide attempts.

Drug Interactions

Certain drugs of abuse and certain medications used in detoxification may interact with others. Thus, it is important to be aware of any other medications that the patient is taking and to consider potential drug interactions. Some examples of dangerous combinations include hypertensive medication and clonidine, phenytoin (Dilantin) and methadone, and rifampin and methadone.

Patient Comfort and Care

Supportive and hygienic care must be provided. Staff should provide whatever assistance is necessary to help the patient get cleaned up as much as possible immediately after entering the facility and bathed thoroughly as soon as he or she has been medically stabilized. Dental and oral care should be made available. The staff should carefully assess the patient for trauma, including bruises and lacerations. Because of their decreased level of consciousness, severe alcoholics may not be aware of head injuries, lacerations, and the like. Staff should continue to observe patients for head injuries after admission, because some injuries, such as subdural hematomas, may not be immediately evident.

Withdrawal from Opiates

All opiates, heroin, morphine, hydromorphone (Dilaudid), codeine, and methadone, produce similar withdrawal signs and symptoms. However, the time of onset and the duration of the abstinence syndrome vary. The severity of the withdrawal syndrome depends on many factors, including the drug used, the total daily dose, the interval between doses, the duration of use, and the health and personality of the addict. The

common signs and symptoms of opiate withdrawal are summarized in Exhibit 1.

Symptoms of withdrawal from opiates may be divided into four classes: 1) gastrointestinal distress, including diarrhea and, less frequently, nausea or vomiting; 2) pain, typically either arthralgias or myalgias or abdominal cramping; 3) anxiety; and 4) insomnia.

Opiate Abstinence Syndromes

Signs and symptoms of withdrawal from heroin or morphine begin 8 to 12 hours following the patient's last dose. They subside over a period of 5 to 7 days.

Signs and symptoms of withdrawal from methadone begin 12 hours after the patient's last dose. The peak intensity occurs on the third day of abstinence or later. Symptoms gradually subside, but may continue for 3 weeks or longer. Methadone abstinence syndrome develops more slowly and is more prolonged but usually less intense than other opiate abstinence syndromes.

In July 1993, the FDA approved levo-alpha-acetylmethadol (LAAM) for use as a maintenance medication. It is a Schedule II controlled substance, which categorizes it as a medication with medical uses but also with a high potential for abuse. Few studies have addressed the medically supervised withdrawal of LAAM patients to a drug-free state. Withdrawal from LAAM produces similar symptoms to those produced by withdrawal from methadone.

Medication Treatment for Opiate Withdrawal

Clonidine

Clonidine (Catapres), a medication marketed for the treatment of hypertension, has been used for treatment of the symptoms of opiate withdrawal since 1978 (Gold et al., 1978). Although clonidine has not yet been approved by the FDA for treatment of opiate withdrawal, its use has become standard clinical practice (Alling, 1992).

Exhibit 1	
Signs and Symptoms of Opiate Abstinence	
EARLY	ADVANCED
Anxiety	Insomnia
Increased respiratory rate	Nausea and vomiting
Sweating	Diarrhea
Lacrimation (tearing or crying)	Weakness
Yawning	Abdominal cramps
Rhinorrhea (runny nose)	Tachycardia
Piloerection (goosebumps)	Hypertension
Restlessness	Muscle spasms
Anorexia	Muscle and bone pain
Irritability	
Dilated pupils	

Clonidine has some practical advantages over methadone for treating narcotic withdrawal, particularly in drug-free programs (Clark and Longmuir, 1986). These advantages include

- It is not a scheduled medication
- The use of opiates can be discontinued immediately in preparation for naltrexone induction or admission to a drug-free treatment program (for example, a therapeutic community)
- It does not produce opiate euphoria, and patients' need for drugs is therefore reduced.

Although clonidine alleviates some symptoms of opiate withdrawal, it is not effective for muscle aches, insomnia, or drug craving. These symptoms require additional medication.

An appropriate protocol for clonidine is 0.1 mg administered orally as a test dose (0.2 mg for patients weighing more than 200 pounds). If the patient's symptoms are acute, the sublingual route of administration may be used. Clinicians should check the patient's blood pressure after 45 minutes. If diastolic blood pressure is normal for the patient and the patient has no signs of orthostatic hypotension (a drop in systolic blood pressure of 10 mm hg upon standing), the patient may continue clonidine, 0.1 to 0.2 mg orally every 4 to 6 hours. Clonidine is most effective when used for detoxification in an inpatient setting, as side effects can be monitored more closely.

Clonidine transdermal patch. In 1986, a transdermal patch containing clonidine (Catapres-TTS) was approved for use in the United States for the treatment of hypertension. However, addiction specialists quickly grasped its potential for treatment of opiate withdrawal. Although the clonidine patch is commonly used for detoxification, several panelists and reviewers were concerned that the safety of the patch for treatment of opiate withdrawal has not been sufficiently studied in controlled clinical trials. If patients receive too much clonidine from the patch and become hypotensive, the effects are not rapidly reversed even when the patch is removed. Alling (1992) recommends the use of clonidine only if the patient's blood pressure is monitored regularly.

The clonidine patch is a 0.2 mm square that is applied in the same manner as a self-adhesive bandage. It is available in three sizes: 3.5, 7.0, and 10.5 cm². In a 24-hour period, these patches deliver an amount of clonidine equivalent to twice-daily dosing with 0.1, 0.2, or 0.3 mg of oral clonidine, respectively. Once the patch is placed on the epidermal surface, clonidine enters the circulatory system through the skin. A rate-limiting membrane within the patch governs the maximum amount absorbed. The patch supplies clonidine for up to 7 days. One application of the patch is sufficient.

In a recovery-oriented treatment program, the transdermal patch offers some advantages over oral clonidine. First, it minimizes drug cravings. Nurses in chemical dependency units often interpret patient requests for medications differently than do nurses in a medical or surgical hospital. In a chemical dependency unit, nurses often perceive these requests as drug-seeking behavior, and the result may be a confrontation with the patient about whether or not the medication is needed. For this reason, the use of "as needed" medications should be minimized.

A second advantage of the transdermal patch is that it eliminates disruptions caused by administration of medication. Oral clonidine must be administered several times each day, and chemical dependency counselors often report that groups or counseling sessions are disrupted when patients leave to obtain their medication.

The patch overcomes the problem of missed doses. Asymptomatic patients may forget to go to nurses' stations at scheduled times or miss doses when they are attending outside activities.

The patch also prevents the buildup of withdrawal symptoms during the night. Patients who miss doses of oral clonidine during the night because the nurses are reluctant to wake them sometimes experience opiate withdrawal upon awakening. The patch continues to deliver clonidine throughout the night.

For reasons such as these, staff and patients often prefer the patch over oral clonidine. Patients treated with oral clonidine appear to have more withdrawal symptoms than those treated with transdermal patches. However, controlled studies have not yet confirmed these findings.

Methadone

Methadone can be used for withdrawal from heroin, fentanyl, or any other opiate. For certain patient populations, including those with many treatment failures, methadone is the treatment of choice. Methadone generally is not used with adolescents because FDA regulations prohibit its use with this age group (except in rare exceptions). In this population, there are high risks of addiction and promotion of drug-seeking behavior.

This TIP focuses on the use of methadone for detoxification. For detailed information readers are referred to the TIPs *State Methadone Treatment Guidelines* and *Matching Treatment to Patient Needs in Opioid Substitution Therapy*.

Opiate-dependent inpatients who are being treated for an acute medical illness can be administered methadone for prevention of opiate withdrawal if opiate withdrawal would complicate treatment of their medical conditions. The withdrawal protocols using methadone vary, depending on the setting.

Inpatient drug treatment program licensed for methadone detoxification. A starting dose of 30 to 40 mg per day of oral methadone is adequate to prevent severe withdrawal symptoms in most opiate-dependent patients. The methadone is administered four times daily, beginning with 10 mg doses, and the patient is observed for 2 hours following each dose. If the patient is sleepy, the next dose is decreased to 5 mg. If the patient shows *objective* signs of opiate withdrawal, the dose is increased to 15 mg. After 24 hours, the methadone is withdrawn by 5 mg per day; thus, most patients are withdrawn over 8 days.

Outpatient methadone detoxification clinics. In an outpatient clinic, treatment staff usually administer medication no more than twice a day. Thus 20 mg of methadone, given orally twice daily, is a good starting point. To prevent an unacceptable level of withdrawal symptoms, some outpatients may need up to 60 mg of methadone per day administered in divided doses. After the second day, the methadone is tapered by 2.5 mg per day.

Federal regulations governing methadone detoxification. As of 1989, Federal regulations allow short-term methadone detoxification of 30 days and long-term detoxification of 180 days. As the State methadone licensing agencies develop regulations that parallel the Federal regulations, State-licensed methadone programs can implement long-term methadone detoxification.

Federal regulations allow physicians to administer (but not prescribe) narcotics for the purpose of relieving acute withdrawal symptoms while arrangements are being made for referral for treatment. Not more than 1 day's medication may be administered to the person or for the person's use at one time. Such emergency treatment may be carried out for not more than 3 days and may not be renewed or extended (21 C.F.R. Part 1306.07). Thus, under Drug Enforcement Administration (DEA) guidelines, in States that allow the prescription of narcotics, a physician may administer methadone for 3 days without a special license if the patient is experiencing acute withdrawal symptoms and cannot be

immediately referred for treatment. This is considered an emergency situation.

Short-term detoxification. In a short-term detoxification regimen, patients are not allowed to take their methadone home. The initial treatment plan and periodic treatment plan evaluation required for maintenance patients are not necessary; however, the program must assign a primary counselor to monitor a patient's progress toward the goal of short-term detoxification and to provide a drug treatment referral.

A patient is required to wait at least 7 days between concluding a short-term detoxification treatment episode and beginning another. Before a short-term detoxification attempt is repeated, the program physician must document in the patient's record that the patient continues to be or is again physiologically dependent on narcotics. These requirements apply to both inpatient and outpatient short-term detoxification treatment.

Long-term detoxification. Federal methadone treatment guidelines define long-term detoxification treatment as longer than 30 days but not in excess of 180 days. For long-term detoxification, the opioid must be administered by the program physician or by an authorized agent who is supervised by and under the orders of the physician. The drug must be administered on a regimen designed to help the patient reach a drug-free state and to make progress in rehabilitation in 180 days or fewer. The following conditions apply:

- During detoxification, the patient must be under observation while ingesting the methadone for at least 6 days a week.
- Before long-term detoxification can begin, the program physician must document in the patient's record that short-term detoxification is not a sufficiently long enough treatment course to provide the patient with the additional program services that will be necessary for the patient's rehabilitation.
- An initial drug screen is required for each patient. At least one additional random urine test or analysis must be performed monthly.
- An initial treatment plan and monthly treatment plan evaluation are required.
- A patient is required to wait at least 7 days after concluding a long-term treatment episode before beginning another. Before a long-term detoxification attempt is repeated, the program physician must document in the patient's record that the patient continues to be or is again physiologically dependent on narcotic drugs.

These requirements apply to both inpatient and ambulatory long-term detoxification treatment.

In a critical study published in 1977, Senay et al. suggested that "a slow rate of withdrawal, extending 6 or more months, may result in a greater percentage of patients reaching abstinence and maintaining a drug-free status." However, the 180-day detoxification protocol has not received adequate study. More research is needed to compare its effectiveness with that of shorter regimens. Also, the issue of appropriate dosage is still under investigation. A randomized, double-blind clinical trial comparing the effect of 80 mg to 40 mg doses of methadone in patients enrolled in a 180-day program did not show statistically significant differences in retention between the two dosage levels (Banys et al., 1994).

LAAM

As mentioned previously, in July, 1993 the FDA approved LAAM for use as a *maintenance* medication. The trade name of LAAM is ORLAAM. A detailed discussion of the use of LAAM is presented in the TIP entitled *LAAM in the Treatment of Opiate Addiction*.

Until August, 1993, LAAM was a Schedule I controlled substance, which is defined as a drug with a high abuse potential but with no recognized medical use. In August, 1993 the DEA reclassified it as a Schedule II controlled substance, defined as a medication with medical uses as well as a high potential for abuse (21 C.F.R. Part 1308).

FDA methadone regulations have been revised (58 *Fed. Reg.* 38706 Part July 20, 1993) to allow use of LAAM (21 C.F.R. Part 291). The regulations for LAAM are similar to those for methadone, with two exceptions: take-home doses of LAAM are not allowed, and LAAM cannot be administered to pregnant women. Patients who need take-home doses must be switched to methadone. Like methadone, LAAM may be dispensed only by licensed AOD abuse treatment clinics (21 C.F.R. 291.505).

LAAM is a prodrug with little opiate activity. This means that its opiate effects are produced by its long-acting metabolites, nor-LAAM and dinor-LAAM. Since LAAM itself is not a potent opiate, oral ingestion or intravenous injection of LAAM does not produce rapid onset of opiate effects as does the ingestion of methadone, heroin, morphine, and most other opiates.

Discontinuation from LAAM maintenance. The metabolites of LAAM are long-acting, and gradual discontinuation of LAAM will result in a slow decline in the plasma levels of nor-LAAM and dinor-LAAM and in the emergence of opiate withdrawal symptoms. Maintenance treatment with LAAM produces significant levels of dependence of the opiate type; therefore, discontinuation of LAAM requires management of opiate withdrawal. Few studies have addressed the medically supervised withdrawal of LAAM patients to a drug-free state. However, no evidence exists to suggest that withdrawal from LAAM is different than withdrawal from methadone or any other opioid. Because LAAM is longer acting than methadone, withdrawal will have a delayed onset and protracted course, although it may be less intense than withdrawal from methadone. Patients, however, tend to perceive a longer period as being "worse," whether the actual intensity of symptoms is greater or not. Special counseling may be needed to address this aspect of withdrawal from LAAM.

The LAAM dose can be reduced gradually at a rate determined by the patient's response. As an alternative, patients who want to withdraw from LAAM treatment can be converted to methadone (at 80 percent of their LAAM dose) with minimal difficulty (Ling et al., 1980). The key consideration may be the patient's support system; take-home methadone entails fewer clinic visits. Although patients can visit the clinic on nondose days for support services only, they are less likely to do so without the incentive of receiving medication. Another option is the use of clonidine in the dosage regimen described previously for

treatment of heroin withdrawal, to assist in discontinuing use of LAAM. When involuntary withdrawal from medication is unavoidable, patients should switch to methadone before withdrawal begins.

Heroin Detoxification with LAAM. Although there is substantial medical literature reporting clinical trials with LAAM in treatment of heroin withdrawal, the FDA has not approved LAAM for use in heroin detoxification. It should, therefore, be used for heroin detoxification only under an Investigational New Drug (IND) exemption. Because LAAM takes from 8 to 12 hours to produce significant opiate effects, it is not a good choice for treatment of acute heroin withdrawal symptoms. Addicts may become impatient while waiting for LAAM to relieve their opiate withdrawal symptoms and may self-medicate their withdrawal symptoms with heroin. As the opiate effects of LAAM develop, the combined effects of heroin and LAAM may result in a life-threatening overdose. Treatment providers may prefer to begin heroin detoxification by stabilizing the patient on methadone, then switch to LAAM for gradual discontinuation over 21 to 180 days. LAAM's long duration of effect makes it a logical option for this process. Additional research to determine how to optimally use LAAM for detoxification is necessary.

Current Problems with LAAM. In the later 1990's numerous reports of physical problems and difficulties associated with the use of LAAM resulted in ORLAAM® being withdrawn from the European market in March 2001. Extensive changes, including additional warnings and contraindications, were made to the U.S. package insert in April 2001, but the compound was still in widespread use.

Roxane Laboratories announced the discontinuation of its distribution of ORLAAM on August 23, 2003, due in large measure to reports of severe cardiac-related adverse events, including slowing of cardiac induction (QT interval prolongation) and cardiac arrest.

Buprenorphine

The FDA has approved buprenorphine for the treatment of pain, and it is being investigated as a treatment for opiate dependence and detoxification. Buprenorphine is a potent analgesic that is available by prescription as a sublingual tablet in many parts of the world. In the United States, it is available by prescription as an analgesic in an injectable form (Buprenex). The doses of buprenorphine under investigation for maintenance treatment are considerably higher than those commonly prescribed for treatment of pain.

Buprenorphine has an unusual pharmacological profile that makes it attractive for the treatment of opiate dependence, and its potential was recognized as early as 1978 (Jasinski et al., 1978). The level of physical dependence produced by buprenorphine is not as great as that produced by methadone or heroin; therefore, most patients find buprenorphine easier to discontinue than methadone. Some patients can eventually be switched from buprenorphine maintenance to treatment with an opiate antagonist such as naltrexone.

Buprenorphine is safer than methadone or LAAM if an overdose is ingested. Its opiate effects appear to plateau at 16 mg (Walsh et al., 1994). Although it is used intravenously by heroin addicts in countries where the sublingual tablet is legally available as an analgesic (San et al., 1992), its abuse potential appears to be substantially less than that of methadone or heroin. And though it is currently an experimental drug with regard to its use in detoxification, buprenorphine may soon be approved by the FDA.

Discontinuation from buprenorphine maintenance. Buprenorphine produces physical dependence of the opiate type. The dosages of patients who have been maintained on buprenorphine for treatment of opiate dependence or chronic pain must be tapered. The onset of withdrawal symptoms is generally delayed for at least 24 hours, and peak intensity of withdrawal symptoms may not occur for 5 days or more. The intensity of withdrawal symptoms is generally less than that following methadone discontinuation. Buprenorphine can be discontinued by tapering the dosage to zero over 7 to 21 days. Symptoms also may be ameliorated with clonidine, particularly toward the end of the taper (Pickworth et al., 1993).

Buprenorphine for heroin detoxification. Buprenorphine has been used successfully to detoxify heroin addicts in a number of clinical trials (Bickel et al., 1988) and to assist with methadone discontinuation (Banys et al., 1994).

In 1985, buprenorphine was classified as a Schedule V narcotic (21 C.F.R. 1308.15(b)). A narcotic is defined by the Controlled Substance Act of 1984 as a class of drugs containing opiates and cocaine, 21 U.S.C. 802(17). The narcotic classification is important because Federal law permits prescription of a narcotic to narcotic addicts only in specially licensed treatment programs (21 C.F.R. 291.505). The sole exception is that when a patient is admitted to a hospital for treatment of an acute medical condition (not solely addiction to drugs) he or she may be administered narcotics to prevent opiate withdrawal.

Because buprenorphine has already been approved by the FDA for treatment of pain, physicians could use it in clinical practice, even for unapproved indications, if it were not classified as a narcotic. Until buprenorphine receives FDA approval for treatment of opiate dependence, it should be prescribed for opiate dependence only under an FDA-approved IND exemption. Physicians may be prosecuted for prescribing, dispensing, or administering buprenorphine for treatment of opiate dependence or withdrawal. State medical licensing boards also may discipline physicians for prescribing buprenorphine for treatment of opiate dependence, absent an IND.

Under investigation. Sublingual tablets containing naloxone and buprenorphine are under investigation for use as treatments for opiate dependency. Since the opiate antagonist naloxone would block the immediate effect of buprenorphine, the combination would be less subject to abuse than buprenorphine alone. If patients dissolve the sublingual tablets, mix them with naloxone, and inject them, they would get no immediate opiate effects. Some buprenorphine opiate effects would eventually occur, however,

because naloxone is more rapidly metabolized than buprenorphine. If a dosage form can be developed that minimizes the potential for diversion, buprenorphine could become the first opiate maintenance medication that could be prescribed as part of general medical practice.

Dextropropoxyphene

In the 1970s, dextropropoxyphene (Darvon) was among the medications used for opiate withdrawal. Because of abuse of dextropropoxyphene by addicts, the DEA reclassified it as a Schedule IV narcotic, narcotic, 21 C.F.R. Part 1308 (1980). The narcotic classification prohibits its use for treatment of opiate dependency in routine clinical practice.

Terminating Opiate Maintenance Treatment

Patients on opiate maintenance are sometimes discontinued from medication for disciplinary reasons. This situation is often awkward for both the program and the patient, particularly if the patient is abusive, threatening, and/or potentially violent.

Involuntary Termination of Opiate Maintenance

The program manager should develop and post prominently on the program premises at least one copy of a written policy covering criteria for involuntary termination from treatment. This policy should describe patients' rights and responsibilities as well as those of program staff. At the time a patient enters treatment, a staff member designated by the program director should inform the patient about the policy and where it is posted. The staff person should inform patients of the conditions under which they might be involuntarily terminated from treatment and of their rights under the termination procedure.

The medication discontinuation should not occur so rapidly that the patient experiences severe opiate withdrawal symptoms. Treatment staff should taper the methadone dosage until the patient is receiving 30 to 40 mg a day. At this point, treatment with clonidine and other medications may begin.

Voluntary Termination of Opiate Maintenance

Patients in methadone treatment, like others who are receiving daily medication on a long-term basis, should be evaluated periodically regarding the risks and benefits of their therapy. For some persons, eventual withdrawal from methadone maintenance is a realistic goal.

Research and clinical experience have not yet identified all the critical variables that determine when a patient can be withdrawn from methadone and remain drug-free. A decision to withdraw voluntarily from methadone maintenance must, therefore, be left to the patient and to the clinical judgment of the physician. Staff should encourage the patient to remain in the program for as long as necessary.

Patient Care and Comfort

Patient care guidelines are similar to those for patients withdrawing from alcohol. Patient comfort is a primary consideration during detoxification, regardless of the detoxification agent. Medications recommended for symptomatic relief of opiate withdrawal are summarized in Exhibit 2.

A complete physical examination should be conducted. The patient should be checked for tuberculosis; symptoms of acquired immunodeficiency syndrome and opportunistic infections; hepatitis A, B, and C; and sexually transmitted diseases. Patients should be monitored for anxiety, sweating, chills, nutritional intake, diarrhea and gastrointestinal distress, sleep dysfunction, muscle cramps, aches, and bowel function.

Skin care is also important. Guidelines should be in place for management of conditions such as skin and subcutaneous abscesses due to needle use.

A few patients may remain in bed for several hours or for as long as a day during detoxification; however, most do not need to do so. Opiate addicts generally have less cognitive impairment than do alcoholics. During detoxification, they may view videotapes and participate in group activities.

If the patient might be pregnant, appropriate testing is essential. It is important to evaluate the safety of withdrawing a pregnant woman from opiates because of the potential effects on the fetus. Often it is best to put the pregnant patient on methadone maintenance. More on the treatment of pregnant women is found in Chapter 4, Special Populations. Other TIPs in this series, *State Methadone Treatment Guidelines; Pregnant, Substance-Using Women*; and *LAAM in the Treatment of Opiate Addiction* include information on issues specific to pregnant women.

Exhibit 2

Medications Recommended for Symptomatic Relief of Opiate Withdrawal*

- Headache: Acetaminophen (Tylenol), 650 mg every 4 hours if needed
- Muscle, Joint, or Bone Pain: Ibuprofen (Motrin, Advil), 600–800 mg every 6–8 hours
- Anxiety or Insomnia: Hydroxyzine (Vistaril), 25–50 mg every 8 hours
- Abdominal Cramps: Dicyclomine (Bentil), 10 mg every 6 hours
- Constipation: Milk of Magnesia, 30 cc daily every other day
- Indigestion: Antacid (for example, Mylanta), 30 cc between meals and at bedtime
- Loose Stool: Bismuth subcarbonate (Pepto-Bismol), 30 cc after each loose stool up to 8 doses total, for no more than 2 days

*All doses are administered orally.

Alternatives to Medication Acupuncture

While some clinicians consider acupuncture an acceptable primary detoxification treatment for opiate abusers, there are few controlled studies that support this. Acupuncture can be a useful treatment adjunct to methadone or clonidine detoxification. One study found that "Increased use of acupuncture therapy not only may be an effective adjunct to therapy in current programs for patients with persistent craving for alcohol, but also may allow treatment to be extended to a large group of recidivist alcoholics for whom current therapies are not effective" (Bullock et al., 1989).

Auricular (ear) acupuncture has been used in treatment of opiate withdrawal since 1972, and it is done in clinics throughout the world. "The use of auricular acupuncture in treating acute drug withdrawal began in Hong Kong in 1972. It was used sporadically throughout the United States during the 1970s, and some experimentation with acupuncture was conducted at the Haight Asbury Free Clinic in San Francisco (Seymour and Smith, 1987). But it has been at Lincoln Hospital in New York, under the guidance of Michael O. Smith, M.D., director of the hospital's division of substance abuse, that the protocol has been refined and expanded and has taken its firmer root" (Brumbaugh, 1993). It is difficult to conduct rigorous double-blind controlled studies with acupuncture because the acupuncturist must insert the needles into very precise locations.

One study (Washburn et al., 1993) compared standard acupuncture with "sham" acupuncture (needles were inserted into points geographically close to standard points). Dropout rates were high in both groups; however, more subjects were retained in the standard than in the "sham" group. Subjects in the standard group also attended the clinic more frequently. According to Washburn et al. (1993),

Of significance was the finding that lighter users attended the acupuncture clinic more days and over a longer period of time than those with heavier habits. Subjects who injected heroin at least three times a day apparently found that acupuncture did not help relieve withdrawal symptoms or reduce craving and, thus, terminated treatment early. That this was true for subjects in both the standard and sham groups suggests that the heroin users may have had little expectation that a drug-free treatment modality would help them. . . . indeed, we found that individuals who injected heroin at least three times a day were less likely to volunteer to participate in the study than were the lighter users. . . . Some of the clients receiving treatment beyond the detoxification episode were using acupuncture as an adjunct to methadone detoxification and maintenance; others seemed to seek additional treatment to detoxify after relapse to heroin use.

Until controlled clinical data indicate otherwise, acupuncture must be viewed as an adjunctive treatment to detoxification.

Electrostimulation

Although some studies have shown that neuroelectric therapy (NET) reduces the chronic withdrawal period for some opiate abusers (Patterson, 1983), a recent study found that NET is no more effective than use of a placebo in opiate and cocaine detoxification (Gariti et al., 1992). NET is therefore not recommended.

Withdrawal From Benzodiazepines and Other Sedative-Hypnotics

For therapeutic use, barbiturates and the older sedative-hypnotics have been largely replaced by the benzodiazepines. The withdrawal syndromes from benzodiazepines and other sedative-hypnotics are similar, and the pharmacotherapy treatment strategies apply to both. This section focuses on the benzodiazepines and adds information about treatment of other types of sedative-hypnotic dependence when appropriate (Alling, 1992).

Dependence on benzodiazepines and other sedative-hypnotics usually develops in the context of medical treatment. Benzodiazepines have many therapeutic uses: As therapy for some conditions, such as panic disorder, long-term treatment is appropriate medical practice. Physical dependency is sometimes unavoidable. Benzodiazepine dependency that develops during pharmacotherapy is not necessarily a substance use disorder (Alling, 1992). When the dependency results from patients taking the prescribed doses as directed by a physician, the term "therapeutic discontinuation" is preferable to the term "detoxification."

Abusers of heroin and stimulants often misuse benzodiazepines and other sedative-hypnotics, sometimes to the extent that they develop a physical dependence. In such cases, it is appropriate to think of withdrawal from the sedative-hypnotic as detoxification.

Use of either benzodiazepines or sedative-hypnotics at doses above the therapeutic range for a month or more produces physical dependence. Without appropriate medical treatment, withdrawal from benzodiazepines or other sedative-hypnotics can be severe and life threatening. Withdrawal from benzodiazepines or other sedative hypnotics produces a similar withdrawal syndrome, described below under high-dose sedative-hypnotic withdrawal.

Some people will develop withdrawal symptoms after stopping therapeutic doses of benzodiazepines or other sedative-hypnotics after they have been used daily for 6 months or more. With "low-dose" withdrawal, the benzodiazepines and other sedative-hypnotics can produce qualitatively different withdrawal syndromes. These are described as high-dose sedative-hypnotic withdrawal syndrome and low-dose benzodiazepine withdrawal syndrome.

High-Dose Sedative-Hypnotic Withdrawal Syndrome

Signs and symptoms of high-dose sedative-hypnotic withdrawal include anxiety, tremors, nightmares, insomnia, anorexia, nausea, vomiting, orthostatic hypotension, seizures, delirium, and hyperpyrexia. The syndrome is qualitatively similar for all sedative-hypnotics; however, the time course of symptoms depends upon the particular drug. With short-acting sedative-hypnotics (for example, pentobarbital [Nembutal], secobarbital [Seconal], meprobamate [Miltown, Equanil], and methaqualone) and short-acting benzodiazepines (for example, oxazepam [Serax], alprazolam [Xanax], and triazolam [Halcion]), withdrawal symptoms typically begin 12 to 24 hours after the last dose and reach peak intensity between 24 and 72 hours after the last dose. Patients who have liver disease or who are elderly may develop symptoms more slowly because of decreased drug metabolism. With long-acting drugs (for example, phenobarbital, diazepam [Valium], and chlordiazepoxide [Librium]), withdrawal symptoms peak on the fifth to eighth day after the last dose.

The withdrawal delirium may include confusion and visual and auditory hallucinations. The delirium generally follows a period of insomnia. Some patients may have only delirium, others only seizures; some may have both.

Low-Dose Benzodiazepine Withdrawal Syndrome

In the literature of addiction medicine, low-dose benzodiazepine withdrawal syndrome may be referred to as "therapeutic-dose withdrawal," "normal-dose withdrawal," or "benzodiazepine-discontinuation syndrome." Knowledge about low-dose dependency is based on clinical observations and is still sketchy and controversial. As a practical matter, often it is impossible to know with certainty whether symptoms are caused by withdrawal or

whether they mark a return of symptoms that were ameliorated by the benzodiazepine. Patients who are treated with benzodiazepines may have had symptoms such as anxiety, insomnia, or muscle tension before taking the benzodiazepine. When they stop taking the benzodiazepine, these symptoms may reappear.

Some people who have taken benzodiazepines in therapeutic doses for months to years can abruptly discontinue the drug without developing symptoms. Others, taking similar amounts of a benzodiazepine, develop symptoms ranging from mild to severe when the benzodiazepine is stopped or the dosage is substantially reduced.

The risk factors associated with withdrawal are not completely understood. Patients who develop the severe form of low-dose benzodiazepine withdrawal syndrome include those with a family or personal history of alcoholism, those who use alcohol daily, or those who concomitantly use other sedatives. According to one study, "higher doses of benzodiazepine lead to increases of withdrawal severity." This study found that the short-acting, high-potency benzodiazepines appear to produce a more intense low-dose withdrawal syndrome than the long-acting, low-potency ones (Rickels et al., 1990).

During the 1980s, many clinical studies and case reports were published concerning withdrawals that were attributed to therapeutic dose discontinuation. Most patients experienced only a transient increase in symptoms for 1 to 2 weeks after termination of the benzodiazepine. This transient increase in symptoms is known as "symptom rebound" and is defined as an intensified return of the symptoms (for example, insomnia or anxiety) for which the benzodiazepine was prescribed. According to the American Psychiatric Association (APA) (1990), "The most immediate discontinuance symptoms tend to be a rebound worsening of the original symptoms. A more severe withdrawal syndrome consists of the appearance of new symptoms, including perceptual hyperacusis, psychosis, cerebellar dysfunction, and seizures." Original symptoms may reappear when the therapeutic medication is withdrawn, and it may be difficult to distinguish recurrence of original symptoms from rebound.

Because of psychiatrists' concerns about benzodiazepine dependency, the APA formed a task force to review these issues. The task force's conclusions (American Psychiatric Association, 1990) were unambiguous about therapeutic dose dependency:

Physiological dependence on benzodiazepines, as indicated by the appearance of discontinuance symptoms, can develop with therapeutic doses. Duration of treatment determines the onset of dependence when typical therapeutic anxiolytic doses are used: clinically significant dependence indicated by the appearance of discontinuance symptoms usually does not appear before four months of such daily dosing. Dependence may develop sooner when higher anti-panic doses are taken daily.

Protracted Withdrawal, Severe Form

A few patients experience a severe, long-lasting withdrawal syndrome, which includes symptoms such as paresthesia and psychoses, never experienced before the benzodiazepines were taken. It is this condition, which may be quite disabling and may last many months, that has generated much of the concern about the long-term safety of the benzodiazepines. However, many psychiatrists believe that the symptoms that occur after discontinuation of therapeutic doses of benzodiazepines are not a withdrawal syndrome but a reemergence or unmasking of the patient's psychopathology.

Protracted Withdrawal, Mild Form

One additional form of withdrawal is sometimes attributed to the benzodiazepines and other sedative-hypnotics as well as to alcohol and opiates. This is a mild form of protracted withdrawal. Its symptoms include irritability, anxiety, insomnia, and mood instability. The symptoms may persist for months following the beginning of abstinence (Geller, 1991).

Medication Treatment for Benzodiazepine Withdrawal

The physician's response during benzodiazepine withdrawal is critical to a successful outcome. Some physicians interpret patients' escalating symptoms as evidence of their need for additional benzodiazepine treatment. Consequently, they prescribe a benzodiazepine, often at higher doses, or switch the patient to another benzodiazepine. Reinstitution of any benzodiazepine agonist may not achieve satisfactory symptom control and may in fact prolong the recovery process.

Another common response is to declare patients addicted to benzodiazepines and refer them to primary chemical dependency treatment. Such a referral is not appropriate unless the patient has a substance use disorder.

Treatment of High-Dose Benzodiazepine Withdrawal

Selection of the withdrawal medication. Abrupt discontinuation of a sedative-hypnotic in patients who are severely physically dependent on it can result in serious medical complications and even death. For this reason, medical management is always needed, and treatment is best provided in a hospital. There are three general medication strategies for withdrawing patients from sedative-hypnotics, including benzodiazepines: (1) the use of decreasing doses of the agent of dependence; (2) the substitution of phenobarbital or another long-acting barbiturate for the addicting agent and the gradual withdrawal of the substitute medication (Smith and Wesson 1970, 1971, 1983, and 1985); and (3) the substitution of a long-acting benzodiazepine, such as chlordiazepoxide (Librium), which is tapered over 1 to 2 weeks. The method selected depends on the particular benzodiazepine, the involvement of other drugs of dependence, and the clinical setting in which detoxification takes place.

Gradual reduction of the agent of dependency. This is an appropriate strategy for managing patients who (1) are taking long-acting medications such as chlordiazepoxide (Librium) or diazepam (Valium); (2) can be expected to give accurate accounts of their use of medication; and (3) are not concurrently abusing alcohol or other drugs (Alling, 1992).

Phenobarbital substitution. The phenobarbital method is the most generally applicable. The pharmacologic rationale for phenobarbital substitution is that this agent is long-acting and produces little change in blood levels between doses. This allows the safe use of a progressively smaller daily dose. Phenobarbital is safer than the shorter-acting barbiturates; lethal doses of phenobarbital are many times higher than toxic doses, and the signs of toxicity (for example, sustained nystagmus, slurred speech, and ataxia) are easily observable. Finally, phenobarbital intoxication usually does not produce disinhibition; consequently, most patients view it as a medication, not as a drug of abuse.

Discontinuation of the benzodiazepine of dependence occurs primarily in medical settings. The patient must be cooperative, be able to adhere to dosing regimens, and not be abusing AODs.

Stabilization. Substituting phenobarbital is the best choice for patients who have lost control of their benzodiazepine use or who are polydrug dependent. Phenobarbital substitution has the broadest use for all sedative-hypnotic drug dependencies and is widely used in drug treatment programs. For that reason, this approach will be described in detail. The patient's history of drug use during the month before treatment is used to compute the stabilization dose of phenobarbital. Although many patients exaggerate the number of pills they are taking, the patient's history is the best guide to initiating pharmacotherapy for withdrawal. Patients who have overstated the amount of drug they have taken will become intoxicated during the first day or two of treatment. The treatment provider can easily manage intoxication by omitting one or more doses of phenobarbital and recalculating the daily dose.

The patient's average daily sedative-hypnotic dose is converted to phenobarbital equivalents, and the daily amount is divided into three doses. (See Exhibits 3 and 4 for a list of benzodiazepines and other sedative hypnotics and their phenobarbital withdrawal equivalents.) The computed phenobarbital equivalence dosage is given in three or four doses daily. If the patient is using significant amounts of other sedative-hypnotics, including alcohol, the amounts of all the drugs are converted to phenobarbital equivalents and added. (For example, 30 cc of 100-proof alcohol are equated to 30 mg of phenobarbital for withdrawal purposes.) Before receiving each dose of phenobarbital, the patient is checked for signs of phenobarbital toxicity (sustained nystagmus, slurred speech, or ataxia). Of these, sustained nystagmus is the most reliable. If nystagmus is present, the scheduled dose of phenobarbital is withheld. If all three signs are present, the next two doses of phenobarbital are withheld, and the daily dosage of phenobarbital for the following day is reduced by half.

**Exhibit 3
Benzodiazepines and Their Phenobarbital Withdrawal Equivalents**

GENERIC NAME	TRADE NAME	THERAPEUTIC DOSE RANGE (MG/DAY)	DOSE EQUAL TO 30 MG OF PHENOBARBITAL FOR WITHDRAWAL (MG)**	PHENOBARBITAL CONVERSION CONSTANT
Benzodiazepines				
alprazolam	Xanax	0.75-6	1	30
chlordiazepoxide	Librium	15-100	25	1.2
clonazepam	Klonopin	0.5-4	2	15
clorazepate	Tranxene	15-60	7.5	4
diazepam	Valium	4-40	10	3
estazolam	ProSom	1-2	1	30
flumazenil	Mazicon	***	***	***
flurazepam	Dalmane	15-30*	15	2
halazepam	Paxipam	60-160	40	0.75
lorazepam	Ativan	1-16	2	15
midazolam	Versed	***	***	***
oxazepam	Serax	10-120	10	3
prazepam	Centrax	20-60	10	3
quazepam	Doral	15*	15	2
temazepam	Restoril	15-30*	15	2
triazolam	Halcion	0.125-0.50*	0.25	120

* Usual hypnotic dose

** Phenobarbital withdrawal conversion equivalence is not the same as therapeutic dose equivalency. Withdrawal equivalence is the amount of the drug that 30 mg of phenobarbital will substitute for and prevent serious high-dose withdrawal signs and symptoms.

*** Not applicable

Information in this exhibit is drawn from two sources, the American Psychiatric Association and the work of Donald R. Wesson, et al. Portions of the exhibit are reprinted with permission from the *American Psychiatric Press Textbook of Substance Abuse Treatment*, Washington, D.C. 1990.

Exhibit 4
Other Sedative-Hypnotics and Their Phenobarbital Withdrawal Equivalents

GENERIC NAME	NAME(S)	COMMON THERAPEUTIC INDICATION	DOSE EQUAL TO 30 MG OF THERAPEUTIC DOSE RANGE (MG/DAY)	PHENOBARBITAL FOR WITHDRAWAL (MG)**	CONVERSION CONSTANTS
Barbiturates					
amobarbital	Amytal	sedative	50-150	100	0.33
butabarbital	Butisol	sedative	45-120	100	0.33
butalbital	Fiorinal, Sedapap	sedative/analgesic*	100-300	100	0.33
pentobarbital	Nembutal	hypnotic	50-100	100	0.33
secobarbital	Seconal	hypnotic	50-100	100	0.33
Others					
bupirone	Buspar	sedative	15-60	***	***
chloral hydrate	Noctec, Somnos	hypnotic	250-1000	500	0.06
ethchlorvynol	Placidyl	hypnotic	500-1000	500	0.06
glutethimide	Doriden	hypnotic	250-500	250	0.12
meprobamate	Miltown, Equanil, Equagesic	sedative	1200-1600	1200	0.025
methylprylon	Noludar	hypnotic	200-400	200	0.15

* Butalbital is usually available in combination with opiate or non-opiate analgesics.

** Phenobarbital withdrawal conversion equivalence is not the same as therapeutic dose equivalency. Withdrawal equivalence is the amount of the drug that 30 mg of phenobarbital will substitute for and prevent serious high-dose withdrawal signs and symptoms.

*** Not cross-tolerant with barbiturates.

Information in this exhibit is drawn from two sources, the American Psychiatric Association and the work of Donald R. Wesson, et al. Portions of the exhibit are reprinted with permission from the *American Psychiatric Press Textbook of Substance Abuse Treatment*, Washington, D.C., 1990.

If the patient is in acute withdrawal and has had or is in danger of having withdrawal seizures, the initial dose of phenobarbital is administered by intramuscular injection. If nystagmus and other signs of intoxication develop 1 to 2 hours following the intramuscular dosage, the patient is in no immediate danger from barbiturate withdrawal. Patients are maintained on the initial dosing schedule of phenobarbital for 2 days. If the patient displays neither signs of withdrawal nor of phenobarbital toxicity (slurred speech, nystagmus, unsteady gait), phenobarbital withdrawal is begun.

Withdrawal. Unless the patient develops signs and symptoms of phenobarbital toxicity or sedative-hypnotic withdrawal, phenobarbital is decreased by 30 mg per day. Should signs of phenobarbital toxicity develop during withdrawal, the daily phenobarbital dose is decreased by 50 percent, and the 30 mg per day withdrawal is continued from the reduced phenobarbital dose. Should the patient have objective signs of sedative-hypnotic withdrawal, the daily dose is increased by 50 percent, and the patient is restabilized before continuing the withdrawal.

Treatment of Low-Dose Benzodiazepine Withdrawal

Clinicians should make decisions regarding the treatment of low-dose withdrawal based on the patient's symptoms. Withdrawal seizures are not usually expected. Patients with an underlying seizure disorder must be maintained on full doses of anticonvulsant medications, and medications that lower seizure threshold should be avoided. Patients may need much reassurance that the symptoms are transient and that with continued abstinence they will eventually subside.

Patients who have the severe form of withdrawal may need psychiatric hospitalization if symptoms become intolerable. Phenobarbital, in doses of 200 mg per day, generally provides considerable reduction in symptoms. Phenobarbital is slowly tapered over several months.

Withdrawal From Stimulants (Cocaine, Crack Cocaine, Amphetamines, and Methamphetamine)

The two most commonly abused stimulants are cocaine and methamphetamine. Intermittent binge use of both agents is common. The withdrawal symptoms that occur after a 2- to 3-day binge are different than those that occur after chronic, high-dose use. The withdrawal syndromes are similar.

Following a 2- to 3-day binge, stimulant abusers are dysphoric, exhausted, and somnolent for 24 to 48 hours. Because cocaine abusers commonly take alcohol, marijuana, or even heroin with cocaine to reduce the irritability caused by high-dose stimulant abuse, the withdrawal may be in response to the combination of drugs. The patient also may have become dependent on more than one drug.

Following regular use, the withdrawal syndrome consists of dysphoria, irritability, difficulty sleeping, and intense dreaming. Often stimulant abusers experience signs and symptoms of the abuse of multiple drugs. The symptoms subside over 2 to 4 days of drug abstinence.

There is no specific treatment for stimulant withdrawal. Mild sedation with phenobarbital or chloral hydrate for sleep may ameliorate patients' distress.

In the medical literature, descriptions of cocaine withdrawal can be confusing because some authors define cocaine craving as a prominent withdrawal symptom. Scientists are not yet certain that craving is a withdrawal symptom. Cocaine craving usually rapidly diminishes in inpatient cocaine abusers when they are unable to get the drug and no longer come in contact with the environmental stimuli associated with cocaine use.

Although the mechanism of drug craving is not well understood, recent studies have demonstrated that environmental and other stimuli can trigger the physiological process of craving (O'Brien et al., 1991). Therefore, exposure to stimuli (which include other drugs) must be controlled.

Withdrawal From Other Drugs

Marijuana

There is no acute abstinence syndrome associated with withdrawal from marijuana. Some patients are irritable and have difficulty sleeping for a few days when they discontinue chronic use of marijuana. Persons withdrawing from marijuana, like those withdrawing from cocaine, benefit from a supportive environment during detoxification.

Nicotine

Two issues regarding tobacco smoking merit consideration by staff of AOD detoxification programs. The first is the program management's desire to establish a smoke-free treatment environment to comply with workplace ordinances and to safeguard the health and comfort of patients from exposure to second-hand smoke. The second issue is the patient's dependence on nicotine as a drug of abuse. Both issues are addressed in a theme issue of the *Journal of Substance Abuse Treatment* entitled "Toward a Broader View of Recovery: Integrating Nicotine Addiction and Chemical Dependency Treatments" (Volume 10, Number 2, March/April 1993).

Many programs have implemented smoke-free environments. Some programs treat nicotine as a drug of abuse and require that patients stop smoking as part of their chemical dependency treatment. A growing number of researchers feel that "the acquisition, spread, and even severity of various drug dependencies may be related to prior or current tobacco use patterns" (Henningfield et al., 1990). Most programs provide education about nicotine and encourage patients to quit smoking. Some provide nicotine patches or other medication to manage physiological withdrawal symptoms.

Hallucinogens

Lysergic acid diethylamide (LSD), dimethyltryptamine (DMT), psilocybin, mescaline, 3,4-methylenedioxy- amphetamine (MDA), and 3,4,- methylenedioxy-methamphetamine (MDMA, also called XTC or "ecstasy") do not produce physical dependence.

Treatment professionals have noted a recent resurgence in the use of hallucinogenic drugs such as LSD, phencyclidine (PCP), and MDMA. These drugs produce no acute withdrawal syndrome.

PCP

Chronic use of PCP can cause a toxic psychosis that takes days or weeks to clear; however, PCP does not have a withdrawal syndrome.

Inhalants/Solvents

Individuals may become physically dependent on hydrocarbons, which include gasoline, glue, and aerosol sprays (including paint, waterproofing material, etc.) and paint thinner. There is clinical evidence that withdrawal from inhalant use is similar to that experienced by persons withdrawing from alcohol. Phenobarbital may be prescribed during detoxification.

Polydrug Use

Addicts rarely use just one drug. Typical combinations and the preferred modes of treatment are shown as follows:

- Alcohol and stimulant: Treat alcohol abuse.
- Alcohol and benzodiazepine: Treat with phenobarbital.
- Cocaine and benzodiazepine: Treat benzodiazepine withdrawal.
- Cocaine and opiate: Treat opiate dependence.
- Cocaine and amphetamine: No detoxification protocol is known.

Opiate-Barbiturate Dependence

Symptoms of withdrawal from opiates and barbiturates have some common features, making it difficult to assess the patient's clinical condition when both drugs are withdrawn at the same time. Many clinicians prefer to gradually withdraw the sedative-hypnotic first, while administering methadone to prevent opiate withdrawal. When the patient is barbiturate-free, the methadone is withdrawn at a level of 5 mg per day. If the sedative-hypnotic was a benzodiazepine (diazepam or chlordiazepoxide), some clinicians prefer to begin with a partial reduction of the sedative-hypnotic. While the patient is still receiving a partial dosage of the sedative, methadone is withdrawn. Finally, the sedative-hypnotic is totally withdrawn.