REVIEW ARTICLE

CURRENT CONCEPTS

Management of Drug and Alcohol Withdrawal

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Each year in the United States, approximately 8.2 million persons are dependent on alcohol and 3.5 million are dependent on illicit drugs, including stimulants (1 million) and heroin (750,000).[1] In a sample from primary care practice, 15 percent of patients had either an "at-risk" pattern of alcohol use or an alcohol-related health problem, and 5 percent had a history of illicit-drug use.[2] With rates of substance use so high, all patients should be carefully screened with validated instruments such as the CAGE questionnaire for alcohol dependence, which consists of the following questions: Can you cut down on your drinking? Are you annoyed when asked to stop drinking? Do you feel guilty about your drinking? Do you need an eye-opener drink when you get up in the morning? Physicians should be prepared to treat patients who have withdrawal syndromes.[3] A carefully taken history should include the time of last use for each substance involved, and toxicologic screening should be performed to identify any additional substances used.

The substances abused must be determined early in treatment, because there are substantial differences in severe complications and in the management of withdrawal from alcohol and sedatives, opiates, and stimulants. Although the initial symptoms of withdrawal — for example, dysphoria, insomnia, anxiety, irritability, nausea, agitation, tachycardia, and hypertension — are similar for all three classes of drugs, complications and therefore treatment can differ greatly. For example, clonidine given to a patient withdrawing from an opioid can mask early symptoms of alcohol or sedative withdrawal and, without specific medication for sedative withdrawal, can lead to seizures. Detoxification is an important first step in substance-abuse treatment. It has three goals: initiating abstinence, reducing withdrawal symptoms and severe complications, and retaining the patient in treatment. Ongoing treatment is needed thereafter to maintain abstinence.

Pharmacologic treatment of drug withdrawal often involves substituting a long-acting agent for the abused drug and then gradually tapering its dosage. The desirable qualities for outpatient medications include administration by mouth, low potential for abuse and overdose, and low incidence of side effects.[4] Adequate dosages of appropriate substitute medications are important. Patients often safely attain abstinence without pharmacologic interventions, however, and the threshold for pharmacotherapy differs among abused drugs. The need for medication is signaled by both symptoms and signs in patients withdrawing from alcohol, by severe objective signs in those withdrawing from stimulants, and by specific signs during withdrawal in those withdrawing from opioids. For patients addicted to heroin, sustained opioid stabilization is often a better treatment option than detoxification and abstinence.

Outpatient management is appropriate for patients with mild-to-moderate withdrawal symptoms who have no important coexisting conditions and have a support person willing to monitor their progress closely. The emergence of serious complications, including delirium tremens among patients dependent on alcohol or depression with suicidal ideation or psychotic symptoms among patients dependent on stimulants or opioids, demands inpatient treatment. In addition, coexisting psychiatric and medical

disorders must be managed. Care must be supportive and nonjudgmental, yet assertive.

During detoxification, behavioral interventions for ongoing treatment of these chronic relapsing disorders may be started. Such interventions should be more sophisticated than simple referral to self-help groups. Effective treatments include contingency management, motivational enhancement, and cognitive therapies.[5,6]

WITHDRAWAL FROM SEDATIVES (ALCOHOL AND BENZODIAZEPINES)

CLINICAL PRESENTATION AND GENERAL MANAGEMENT

The clinical history often suggests alcohol problems, which are seen in 15 to 20 percent of patients in primary care and hospitalized patients.[7] Since alcohol withdrawal can be complicated by seizures and delirium and is more severe in persons with more previous episodes of withdrawal or other illnesses, careful evaluation is essential. Such evaluation should include assessment for anemia, thrombocytopenia, and elevated liver-enzyme levels.[7,8] Specific symptoms during sedative or alcohol withdrawal that may dictate pharmacotherapy include auditory and tactile disturbances and seizures.

Significant components of the withdrawal syndrome after chronic alcohol use reflect reduced neurotransmission in type A γ-aminobutyric acid pathways and enhanced neurotransmission in glutamate (N-methyl-D-aspartate) pathways.[9] Seizures during withdrawal probably result from this altered neurobiology, but the anticonvulsant medication phenytoin is not an effective treatment for alcohol withdrawal.[8,10] Benzodiazepines are effective, probably owing to cross-tolerance with ethanol at the type A γ-aminobutyric acid receptor, where carbamazepine and divalproate are also believed to have their main actions.[11,12] On the basis of this neurobiology, antagonism at the N-methyl-D-aspartate receptor is another potential mechanism for relieving symptoms of alcohol and sedative withdrawal and may be important for reducing the toxic effects from repeated episodes of alcohol withdrawal.[13]

Withdrawal symptoms can be quantified to allow symptom-triggered therapy, in which the patient receives medication only when symptoms exceed a threshold of severity, rather than on a fixed schedule (Table 1). This approach is as effective as fixed-dose therapy but requires significantly less medication and leads to a more rapid detoxification.[14,15] It does, however, require careful and frequent monitoring with a validated withdrawal-symptom scale such as the Clinical Institute Withdrawal Assessment for Alcohol (see the Appendix). The categories on this scale are sweating, anxiety, tremor, auditory or visual disturbances, agitation, nausea and vomiting, tactile disturbances, headache, and orientation. Total symptom scores of more than 15 on this scale or a history of withdrawal seizures indicates that medications should be started at presentation.

Without medication, alcohol-withdrawal symptoms might be expected to peak about 72 hours after the last use of alcohol, but medications can reduce symptoms within hours. In patients with delirium tremens, management with medication requires high doses of benzodiazepines (e.g., 5 to 10 mg of diazepam by intravenous injection, repeated in two to four hours if seizures occur). Unless delirium is present, medication is typically needed for no more than seven days after the last use of alcohol, although some patients will report withdrawal symptoms, including sleep problems, for several more weeks. Protracted symptoms may precipitate relapse.[16]

Withdrawal from benzodiazepines and other sedatives produces more psychomotor and auto-

Table 1. Medication Treatment for Alcohol Withdrawal.

Class	Examples	Effects
Benzodiazepines (preferably long-acting)*	Chlordiazepoxide, diazepam, oxazepam, lorazepam	Decreased severity of withdrawal symptoms; reduced risk of seizures and delirium tremens
Anticonvulsants	Carbamazepine	Decreased severity of withdrawal symptoms
Adjunctive agents		
Beta-blockers	Atenolol, propranolol	Improvement in vital signs; reduction in craving
Alpha-agonists	Clonidine	Decreased severity of withdrawal symptoms

* Dosing follows one of three strategies. With fixed-dose therapy, a set amount of medication is given at regular intervals (e.g., 50 to 100 mg of chlordiazepoxide four times daily), with the dose tapered from day 4 to day 7. With a loading-dose strategy, a moderate-to-high dose of a long-acting benzodiazepine (e.g., 20 mg of diazepam) is given initially to provide sedation; the level is allowed to decrease through metabolism. With symptom-triggered therapy, the first dose of 5 mg of diazepam is given when the score for symptoms is at least 8 on the Clinical Institute Withdrawal Assessment for Alcohol scale. The severity of symptoms is measured one hour after this and each subsequent dose of diazepam and then at least every eight hours, with the frequency of monitoring increased if symptoms worsen. The dose is adjusted (e.g., from 5 mg of diazepam to 10 mg three times daily) according to the severity of the symptoms.

nomic nervous system signs than does withdrawal from alcohol, and these signs start between 2 and 10 days after abrupt discontinuation. If medications are used, treatment with anticonvulsant drugs such as carbamazepine will need to be continued for about two weeks, and the dose of benzodiazepines gradually tapered.

PHARMACOLOGIC TREATMENT

Benzodiazepines and Barbiturates

Two major reviews of pharmacotherapy for alcohol withdrawal concluded that benzodiazepines are the treatment of choice on the basis of several outcomes, including the severity of the alcohol-withdrawal syndrome, occurrence of delirium and seizures, adverse effects of the medication, and completion of withdrawal, as well as subsequent entry into rehabilitation.[8,12] A meta-analysis comparing benzodiazepines with placebo or with an active control drug included 11 trials, representing a total of 1286 patients.[8] There was more often a clinically significant reduction of symptoms within two days with benzodiazepines than with placebo (common odds ratio, 3.28; 95 percent confidence interval, 1.30 to 8.28).[8]

In addition, in six prospective trials, benzodiazepines, particularly longer-acting ones, were more effective than placebo in reducing the incidence of seizures (risk reduction, 7.7 seizures per 100 patients treated; P=0.003) and delirium (risk reduction, 4.9 cases of delirium per 100 patients treated; P=0.04).[8,10,12,17] However, the potential for abuse is greater with agents that have a rapid onset of action, including diazepam, alprazolam, and lorazepam, than for those with slower onset of action, such as chlordiazepoxide, oxazepam, and halazepam.[18] Although phenobarbital has a low potential for abuse as compared with other barbiturates and is used by about 10 percent of substance-abuse programs in the United States, its use is supported by only a few controlled studies. Furthermore, phenobarbital has a poorer safety profile than benzodiazepines: it can cause respiratory depression when used in high doses or when combined with alcohol, as may happen with outpatients.[19]

Other drugs, particularly carbamazepine, do not differ significantly from the benzodiazepines in terms of adverse events (common odds ratio for adverse events associated with benzodiazepines as compared with carbamazepine, 0.67; 95 percent confidence interval, 0.34 to 1.32). Dropout rates in the first seven days are slightly lower with benzodiazepines (common odds ratio, 0.68; 95 percent confidence interval, 0.47 to 0.97).[20] Thus, a critical issue may be the potential effectiveness of anticonvulsant agents for outpatient treatment in more severe as well as mild-to-moderate alcohol withdrawal.

The treatment of benzodiazepine or barbiturate dependence has involved either tapering dosages of the agent of dependence or substituting a longer-acting benzodiazepine or phenobarbital, with a gradual reduction in dose over a period of two weeks. Tables in Smith and Wesson[21] provide dosage equivalents for use in substituting longer-acting for shorter-acting agents.

Adjuvant Treatments

Although they may be useful as adjuvant treatments, most other agents are unsuitable for use alone during alcohol withdrawal. The phenothiazines and haloperidol reduce signs and symptoms of withdrawal but are significantly less effective than benzodiazepines in preventing delirium (difference in risk, 6.6 cases per 100 patients) and seizures (difference in risk, 12.4 seizures per 100 patients) (P<0.01 for both comparisons).[22] Beta-adrenergic antagonists and clonidine reduce autonomic manifestations of withdrawal but have no known anticonvulsant activity.[23,24] Symptoms of early withdrawal or impeding delirium may be masked by propranolol.[25] Centrally acting alpha-adrenergic agonists such as clonidine ameliorate symptoms in patients with mild-to-moderate withdrawal but probably do not reduce delirium or seizures.[26] They may be used in conjunction with benzodiazepines in patients with coexisting conditions such as coronary artery disease. For benzodiazepine withdrawal, however, they have not found much use even when low therapeutic doses are discontinued.[21]

Anticonvulsant Agents

Although phenytoin has no primary role in the treatment of alcohol-withdrawal symptoms, other anticonvulsant agents, such as carbamazepine, have been in clinical use for this purpose for three decades.[27] Carbamazepine is superior to placebo and equal in efficacy to phenobarbital and oxazepam for patients with mild-to-moderate withdrawal symptoms.[28,29] Carbamazepine has no significant toxic effects on the blood or the liver when used in seven-day protocols for alcohol withdrawal[29,30]; it reduces emotional distress better and permits a faster return to work than does oxazepam.[30] Carbamazepine has well-documented anticonvulsant activity and prevents alcohol-withdrawal seizures in studies in an-

imals, but data from trials in humans are limited.[31] It does not potentiate the central nervous system and respiratory depression caused by alcohol, does not inhibit memory (which occurs with even small doses of benzodiazepines), and has no potential for abuse.[21] However, dizziness, vomiting, and nausea are common side effects, particularly at the initial dose of 800 mg per day. Carbamazepine has not been evaluated for treating delirium tremens.

In a recent study of 136 patients with alcohol-withdrawal symptoms, patients treated with carbamazepine had fewer protracted symptoms than did those receiving lorazepam, five days after the medications were stopped.[32] This difference in symptom levels persisted for a week. Furthermore, relapse to alcohol use during a follow-up period of three months was less common in the carbamazepine group. Adverse effects such as dizziness and incoordination were also less common in the carbamazepine group (7 percent vs. 20 percent). Some early studies have suggested that carbamazepine is efficacious in patients undergoing benzodiazepine withdrawal, but the data are less extensive than are those for alcohol.[21,33]

Valproate may also reduce symptoms of alcohol withdrawal. Data have been reported for a total of approximately 2500 patients. The trials have generally been open-label, and not all have reported seizure rates. Two double-blind, randomized studies have been published, however.[32,34] In these trials, patients treated with 1000 to 1200 mg of valproate for four to seven days had fewer seizures, dropped out less frequently, had less severe withdrawal symptoms, and used less oxazepam than did controls treated with placebo or carbamazepine.

No controlled trials have been published on the use of gabapentin for alcohol-withdrawal symptoms.

WITHDRAWAL FROM OPIOIDS

CLINICAL PRESENTATION

Opioid-withdrawal syndrome resembles a severe case of influenza. In addition, the symptoms include pupillary dilatation, lacrimation, rhinorrhea, piloerection ("gooseflesh"), yawning, sneezing, anorexia, nausea, vomiting, and diarrhea. Seizures and delirium tremens do not occur. Patients who are dehydrated or debilitated can have life-threatening complications.

The time to onset of peak opioid-withdrawal symptoms and their duration after abrupt discontinuation depend on the half-life of the drug involved (Fig. 1). For heroin, symptoms peak within 36 to 72 hours and last for 7 to 10 days, whereas for methadone, symptoms peak at 72 to 96 hours but last for 14 days or more, and for buprenorphine, symptoms are less severe and of shorter duration.[35,36]

TREATMENT

Since the use of opiates for detoxification is legally restricted to inpatient settings and specially licensed outpatient programs, patients in outpatient settings more typically receive clonidine or another adrenergic agent. Recent federal initiatives may loosen the restrictions on the use of buprenorphine, a partial opioid agonist, for the treatment of opioid withdrawal.[3,37,38] A summary of pharmacotherapeutic approaches is given in Table 2.

Opioid Medications

Substitution of a long-acting, orally active opioid such as methadone or buprenorphine is the approach preferred by most patients. Sublingual buprenorphine provides an effective and comfortable withdrawal and transition from heroin to antagonist treatment with naltrexone, and it appears to be superior to clonidine in this regard.[39,40] Buprenorphine starting at 4 to 16 mg daily is equivalent to methadone starting at 20 to 35 mg daily, and the

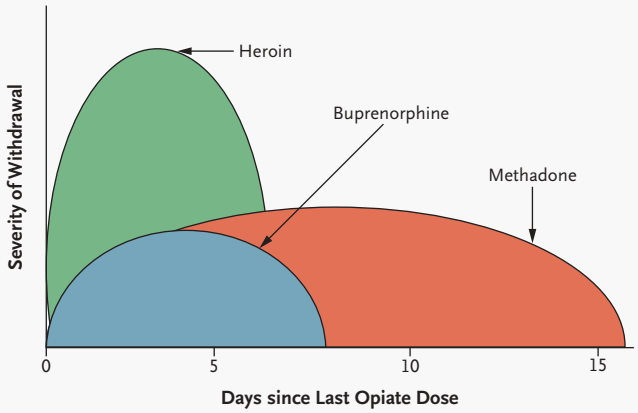

Figure 1. Severity of Opioid-Withdrawal Symptoms after Abrupt Discontinuation of Equivalent Doses of Heroin, Buprenorphine, and Methadone.

Peak withdrawal symptoms are most severe after discontinuation of heroin. Such symptoms last longest with methadone, which has a somewhat later peak of severity. Buprenorphine has milder peak withdrawal symptoms than does methadone; the duration of symptoms is intermediate between those for methadone and those for heroin.

Table 2. Medication Treatment for Opioid Withdrawal.*

Protocol	Examples	Effects and Comments
Medication		
Opioid agonists	Methadone (20 to 35 mg daily) or buprenorphine (4 to 16 mg daily), tapered over several days or weeks	Withdrawal symptoms are decreased in severity. Methadone and other opioid agonists are currently restricted to inpatient settings or licensed programs; buprenorphine is now approved by the FDA for this purpose.
Nonopioid drugs	Clonidine (0.2 mg 3 times daily) or lofexidine (0.2 mg twice daily), administered for approximately 10 days for heroin and 14 days for methadone	Withdrawal symptoms are decreased in severity. Lofexidine is less likely to produce hypotension but is not currently approved by the FDA for this purpose.
Rapid and ultra-rapid detoxification	Protocols include a variety of medications: opioid antagonists (noloxone or naltrexone), clonidine, sedatives, antiemetic agents, analgesics, anesthetics	Withdrawal is precipitated with an opioid antagonist, and symptoms are managed with a variety of adjuvant medications. Patients are awake or lightly sedated for rapid detoxification; they are under heavy sedation or general anesthesia for ultra-rapid detoxification. Both methods require special training, equipment, or both. Research on efficacy is limited.

* FDA denotes Food and Drug Administration.

dose of either medication can be tapered relatively quickly over a period of several days from these initial low doses. If these agents are abruptly discontinued, withdrawal symptoms are more severe and last longer with methadone than with buprenorphine (Fig. 1).

Patients whose methadone dose is reduced each week by 3 percent of the initial dose drop out less frequently, have less illicit opioid use, and have less severe withdrawal symptoms than do patients whose dose is reduced by 10 percent per week, but only 40 percent of the patients in either group achieve abstinence.[41] Reducing the methadone dose from 35 mg over a period of 21 days (a drop of 5 percent per day) offers no advantage in attaining abstinence or relieving withdrawal symptoms over abruptly stopping methadone and substituting clonidine.[42] Even protracted methadone dosage tapering over a period of six months has no greater success than more rapid approaches.[43]

Nonopioid Medications

Opioid drugs are agonists at the μ-opioid receptor, where they inhibit cyclic AMP systems. When chronic opioid use is discontinued, the cyclic AMP system in noradrenergic neurons becomes overactive and noradrenergic brain activity increases, contributing to withdrawal symptoms.[44] These neurons also have adrenergic autoreceptors that, when stimulated by clonidine (or lofexidine), decrease neuronal activity and can reduce opioid-withdrawal symptoms. This discovery is the basis for using clonidine or lofexidine to suppress autonomically mediated signs and symptoms of abstinence.[45] For heroin withdrawal, clonidine is initiated at a dose of 0.1 to 0.2 mg every four hours, which is tapered starting after day 3, with treatment lasting a total of about 10 days. In patients with insomnia or muscle cramps, clonidine can be augmented with a slow-onset, longer-acting benzodiazepine such as chlordiazepoxide.[46] Lofexidine started at 0.2 mg and titrated up to 1.2 mg twice daily is an alternative to clonidine. Patients taking lofexidine are less likely to have hypotension or to drop out of treatment than are those taking clonidine, and they have a more rapid resolution of withdrawal symptoms than do patients taking clonidine.[47] Thus, optimal outpatient treatment might substitute 8 mg of buprenorphine per day for heroin, followed by tapering the dose to 2 to 4 mg of buprenorphine per day and then discontinuing it, and then giving lofexidine or clonidine for about five days.

Rapid and "Ultra-Rapid" Detoxification

The combination of clonidine and the long-acting opioid antagonist naltrexone has been successful with inpatients and outpatients during a five-day protocol.[48] Although withdrawal symptoms during day 1 were more severe in patients taking naltrexone (12.5 mg) plus clonidine than in those taking clonidine alone, the combination produced better results than clonidine alone in primary care settings. In a study of 125 primary care patients, 24 of 57 patients taking clonidine alone (42 percent) and 64 of 68 of those taking both clonidine and naltrexone (94 percent) successfully completed detoxification ($P<0.001$).[46] A more recent randomized clinical trial compared clonidine, clonidine plus naltrexone, and

a new approach using clonidine and naltrexone in combination with buprenorphine.[49] After stabilization for as little as three days, patients taking buprenorphine had less severe withdrawal symptoms than did patients in the other two groups. Rapid detoxification is a very intensive intervention, however, and should only be undertaken by clinicians who have had substantial experience working with simpler approaches to withdrawal, such as using clonidine alone or tapering the dosage of methadone in an inpatient setting. Figure 2 shows the severity and duration of withdrawal with these various approaches. Clearly, withdrawal symptoms are mildest in patients taking clonidine and naltrexone in combination with buprenorphine.

"Ultra-rapid" detoxification is an accelerated (one-day) method of opioid detoxification, in which patients are placed under anesthesia and given naloxone to precipitate acute withdrawal.[50,51] Patients may require intubation and mechanical ventilation during detoxification. A 1998 review critically examined the nine published studies of this technique,[52] only two of which were randomized. Data from a total of 424 patients were included. Only two studies followed patients beyond seven days, and both found rates of longer-term retention in drug treatment to be low.[53,54] Withdrawal symptoms persisting for a week or longer, high cost, and safety are noteworthy problems with this method.[55,56]

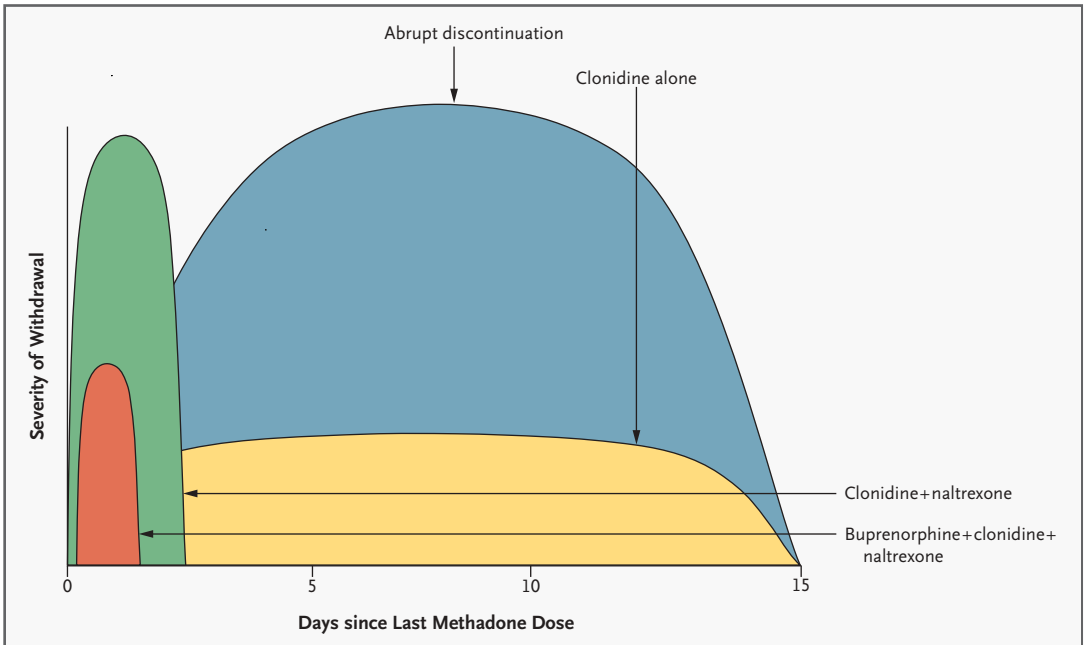

Figure 2. Severity and Duration of Opioid-Withdrawal Symptoms with Three Different Treatments after Abrupt Discontinuation on Day 0 of Methadone at a Dose of about 35 mg Daily.

The blue area represents the natural course of such symptoms after abrupt discontinuation of methadone. The yellow area represents the use of clonidine at 0.1 to 0.2 mg four times per day from days 1 to 7, followed by gradual tapering of the dose from days 8 to 14. The green area represents the precipitation of opioid withdrawal with use of naltrexone at 12.5 mg on day 1, 25 mg on day 2, and 50 mg on days 3 to 15. Clonidine at 0.1 to 0.2 mg four times daily is also given from days 1 to 3, with the dose tapered on days 4 and 5. The red area represents abrupt discontinuation of buprenorphine from a daily dose of 8 mg (equivalent to 35 mg of methadone) and precipitation of opioid withdrawal using naltrexone at 25 mg on day 1 and 50 mg daily on days 2 to 15. Clonidine at 0.1 to 0.2 mg four times daily is also given on day 1, with the dose tapered on days 2 and 3. In patients receiving 35 mg of methadone daily, 8 mg of buprenorphine can be given without precipitating any withdrawal symptoms; buprenorphine should be started at least two days before naltrexone is used to precipitate withdrawal.

WITHDRAWAL FROM STIMULANTS (COCAINE AND AMPHETAMINES)

CLINICAL PRESENTATION

Withdrawal from a stimulant can produce dysphoria with sleep, appetite, and motor disturbances clinically and neurobiologically similar to those seen in depressive disorders.[57,58] Severe depressive symptoms may last only 8 to 48 hours, but milder ones typically persist for approximately two weeks. Although no medications have shown efficacy in reducing the severity of withdrawal symptoms, acute stimulant toxicity characterized by delusions, paranoid thinking, and stereotyped compulsive behavior may require neuroleptic agents or benzodiazepines such as chlordiazepoxide in the first 48 hours after abrupt discontinuation. Because those who are dependent on stimulants are often also dependent on alcohol or heroin, withdrawal symptoms due to the discontinuation of these other substances may require concomitant treatment.

TREATMENT

The monoamine transporter proteins, which act as a reuptake mechanism for terminating synaptic monoaminergic neurotransmission, are blocked by cocaine and amphetamine, leading to massive elevations of synaptic monoamines.[59] Repeated cocaine administration reduces levels of postsynaptic receptors (e.g., dopamine D2 receptors), suggesting a role for dopamine agonists.[60] Direct dopamine agonists such as bromocriptine and pergolide have shown no efficacy. In a three-month double-blind clinical trial, 5 to 7.5 mg of bromocriptine daily was poorly tolerated and was associated with high dropout rates; furthermore, it produced no reduction in subsequent cocaine use.[61] Pergolide also brought about no difference in cocaine use, although pilot work in 21 patients had suggested good response.[62] Indirect dopamine agonists, however, appear to have some efficacy. Methylphenidate, a stimulant and an indirect dopamine agonist, did not decrease cocaine use but was associated with a lower dropout rate than placebo.[63] Amantadine, another indirect dopamine agonist, was compared with placebo in a double-blind trial involving 42 patients treated for 10 days. Urine samples obtained at two-week and one-month follow-up visits were cocaine-free more often in patients taking amantadine than in those taking placebo.[64] Treating more severe cocaine-withdrawal symptoms with propranolol (100 mg daily) may improve treatment retention and reduce cocaine use.[65] The withdrawal symptoms of anxiety and depression have also suggested a role for antidepressants, but these agents have a delayed onset of action and may be useful only after the period of withdrawal is over.[57,60] Table 3 provides a brief listing of pharmacotherapy for stimulant withdrawal; no agents, however, have shown reliable efficacy.

Table 3. Medication Treatment for Stimulant Withdrawal.

Class	Examples	Effects and Comments
Indirect dopamine agonists	Methylphenidate, amantadine	Treatment retention was improved in one study of each agent; data are very limited.
Adrenergic antagonists	Propranolol	Treatment retention was improved and cocaine use was reduced in patients with severe withdrawal symptoms in one study.
Antidepressants	Desipramine, bupropion	Medications are well tolerated but do not appear to be effective during stimulant withdrawal.

THE ROLE OF GENERALIST PHYSICIANS

CLINICAL FEATURES OF PATIENTS

Substance-dependent patients often have other medical and behavioral health problems as well, such as depression and nicotine dependence. The evaluation and treatment of depression are complicated by the overlapping of depressive and withdrawal symptoms, as well as by shared neurobiologic features.[58] Depressive symptoms that persist for more than a week beyond the period of acute withdrawal suggest that treatment with an antidepressant such as a serotonin-reuptake inhibitor may be appropriate.[66] Established antidepressant treatment can be continued during detoxification. For patients who smoke, nicotine-replacement therapy (for example, with a transdermal patch) or bupropion can initiate abstinence and reduce rates of relapse.[67] These interventions are often begun after detoxification from the other three classes of drugs, but nicotine-replacement therapy can be started during other detoxifications. Smoking cessation can be a critical first step in addressing the wide variety of health problems in substance-dependent patients, who also need screening for human immunodeficiency virus infection and liver disease, appropriate immunizations, and assessment for

high-risk sexual activity or physical abuse. Patients found to require additional treatment should be referred for appropriate services. Referrals are also often indicated to social-work, family-counseling, or other social-service agencies.[3]

REFERRAL AS COMPARED WITH DIRECT TREATMENT

Direct treatment in an outpatient setting requires daily contact for several days to monitor progress and adjust doses of medication. Such treatment, delivered by generalist physicians, may be appropriate for highly motivated patients with mild withdrawal symptoms, as long as their social support systems are strong and any coexisting medical or psychiatric conditions are stable. Given the new federal regulations on the use of buprenorphine in office-based settings, generalist physicians may soon be able to provide extended detoxification to certain patients with opioid dependence.[3,8] Patients with moderate-to-severe withdrawal symptoms, poor social support, or substantial medical or psychiatric conditions that go beyond the depressive symptoms characteristic of withdrawal should be referred to specialized outpatient or inpatient programs for withdrawal treatment. Options include outpatient detoxification programs such as methadone tapering for heroin dependence and residential programs providing both medication management and supportive housing. Withdrawal management is only the first step in long-term treatment; follow-up care is always necessary to prevent relapse.

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Appendix. Clinical Institute Withdrawal Assessment for Alcohol.*

Category	Range of Scores	Examples
Agitation	0–7	0=normal activity 7=constantly thrashes about
Anxiety	0–7	0=no anxiety, at ease 7=acute panic states
Auditory disturbances	0–7	0=not present 7=continuous hallucinations
Clouding of sensorium	0–4	0=oriented, can do serial additions 4=disoriented as to place, person, or both
Headache	0–7	0=not present 7=extremely severe
Nausea or vomiting	0–7	0=no nausea, no vomiting 7=constant nausea, frequent dry heaves and vomiting
Paroxysmal sweats	0–7	0=no sweat visible 7=drenching sweats
Tactile disturbances	0–7	0=none 7=continuous hallucinations
Tremor	0–7	0=no tremor 7=severe, even with arms not extended
Visual disturbances	0–7	0=not present 7=continuous hallucinations

* The Clinical Institute Withdrawal Assessment for Alcohol measures 10 categories of symptoms, with a range of scores in each. The maximal score is 67. Minimal-to-mild withdrawal symptoms result in a total score below 8; moderate withdrawal symptoms (marked autonomic arousal), in a total score of 8 to 15; and severe withdrawal symptoms, in a total score of more than 15. High scores are predictive of seizures and delirium.

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