PRACTICE GUIDELINE FOR THE
Treatment of Patients With Substance Use Disorders
Second Edition

WORK GROUP ON SUBSTANCE USE DISORDERS

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CONTENTS

STATEMENT OF INTENT

The American Psychiatric Association (APA) Practice Guidelines are not intended to be construed or to serve as a standard of medical care. Standards of medical care are determined on the basis of all clinical data available for an individual patient and are subject to change as scientific knowledge and technology advance and practice patterns evolve. These parameters of practice should be considered guidelines only. Adherence to them will not ensure a successful outcome for every individual, nor should they be interpreted as including all proper methods of care or excluding other acceptable methods of care aimed at the same results. The ultimate judgment regarding a particular clinical procedure or treatment plan must be made by the psychiatrist in light of the clinical data presented by the patient and the diagnostic and treatment options available.

This practice guideline has been developed by psychiatrists who are in active clinical practice. In addition, some contributors are primarily involved in research or other academic endeavors. It is possible that through such activities some contributors, including work group members and reviewers, have received income related to treatments discussed in this guideline. A number of mechanisms are in place to minimize the potential for producing biased recommendations due to conflicts of interest. Work group members are selected on the basis of their expertise and integrity. Any work group member or reviewer who has a potential conflict of interest that may bias (or appear to bias) his or her work is asked to disclose this to the Steering Committee on Practice Guidelines and the work group. Iterative guideline drafts are reviewed by the Steering Committee, other experts, allied organizations, APA members, and the APA Assembly and Board of Trustees; substantial revisions address or integrate the comments of these multiple reviewers. The development of the APA practice guidelines is not financially supported by any commercial organization.

More detail about mechanisms in place to minimize bias is provided in a document available from the APA Department of Quality Improvement and Psychiatric Services, "APA Guideline Development Process."

This practice guideline was approved in December 2005 and published in August 2006.

GUIDE TO USING THIS PRACTICE GUIDELINE

The *Practice Guideline for the Treatment of Patients With Substance Use Disorders,* 2nd Edition, consists of three parts (A, B, and C) and many sections, not all of which will be equally useful for all readers. The following guide is designed to help readers find the sections that will be most useful to them.

Part A, "Treatment Recommendations for Patients With Substance Use Disorders," is published as a supplement to the *American Journal of Psychiatry* and contains general and specific treatment recommendations. Section I summarizes the key recommendations of the guideline and codes each recommendation according to the degree of clinical confidence with which the recommendation is made. Section II, "General Treatment Principles," provides a general discussion of the formulation and implementation of a treatment plan as it applies to the individual patient. Section II.G, "Clinical Features Influencing Treatment," discusses a range of clinical considerations that could alter the general recommendations discussed in Section I. Sections III, IV, V, VI, and VII provide specific recommendations for the treatment of patients with nicotine-, alcohol-, marijuana-, cocaine-, and opioid-related disorders, respectively.

Part B, "Background Information and Review of Available Evidence," and Part C, "Future Research Needs," are not included in the *American Journal of Psychiatry* supplement but are provided with Part A in the complete guideline, which is available in print format from American Psychiatric Publishing, Inc. (http://www.appi.org) and online through the American Psychiatric Association (http://www.psych.org). Part B provides an overview of substance use disorders, including general information on their natural history, course, and epidemiology. It also provides a structured review and synthesis of the evidence that underlies the recommendations made in Part A. Part C draws from the previous sections and summarizes areas for which more research data are needed to guide clinical decisions.

To share feedback on this or other published APA practice guidelines, a form is available at http://www.psych.org/psych_pract/pg/reviewform.cfm.

DEVELOPMENT PROCESS

This practice guideline was developed under the auspices of the Steering Committee on Practice Guidelines. The development process is detailed in "APA Guideline Development Process," which is available from the APA Department of Quality Improvement and Psychiatric Services. The key features of this process with regard to this document include the following:

- A comprehensive literature review to identify all relevant randomized clinical trials as well as less rigorously designed clinical trials and case series when evidence from randomized trials was unavailable
- The development of evidence tables that summarized the key features of each identified study, including funding source, study design, sample sizes, subject characteristics, treatment characteristics, and treatment outcomes
- Initial drafting of the guideline by a work group that included psychiatrists with clinical and research expertise in substance use disorders
- The production of multiple revised drafts with widespread review (23 organizations and 70 individuals submitted significant comments)
- Approval by the APA Assembly and Board of Trustees
- Planned revisions at regular intervals

Relevant updates to the literature were identified through a MEDLINE literature search for articles published since the initial guideline edition, published in 1995. Thus MEDLINE was searched, using PubMed, between 1995 and 2002 using the keywords "substance use disorder OR substance use disorders OR substance use OR substance withdrawal OR substance intoxication OR substance abuse OR substance dependence OR alcohol abuse OR alcohol dependence OR cocaine abuse OR cocaine dependence OR cocaine use OR marijuana use OR marijuana abuse OR marijuana dependence OR opiate abuse OR opiate dependence OR opiate use OR opioid abuse OR opioid dependence OR opioid use OR heroin abuse OR heroin dependence OR heroin use OR cigarette OR cigarettes OR smoking OR tobacco OR tobacco use OR tobacco use disorder OR tobacco use cessation OR smoking cessation." This search yielded 89,231 references, of which 4,373 were controlled clinical trials; randomized, controlled trials; or meta-analyses; 4,101 of the 4,373 references were studies in humans, were written in the English language, and had abstracts. Evidence tables were developed for these results. Later in the development process, a second MEDLINE literature search, using PubMed, on the same keywords for the period 2003 to February 2005 yielded an additional 25,003 references, of which 1,114 were controlled clinical trials; randomized, controlled trials; or meta-analyses; 1,063 of these 1,114 references were studies in humans, were written in the English language, and had abstracts. Additional, less formal literature searches were conducted by APA staff and individual members of the Work Group on Substance Use Disorders. The Cochrane databases were also searched for relevant meta-analyses.

The summary of treatment recommendations is keyed according to the level of confidence with which each recommendation is made (indicated by a bracketed Roman numeral). In addition, each reference is followed by a bracketed letter that indicates the nature of the supporting evidence.

PART A
TREATMENT RECOMMENDATIONS FOR PATIENTS WITH SUBSTANCE USE DISORDERS

I. EXECUTIVE SUMMARY

► A. CODING SYSTEM

Each recommendation is identified as meriting one of three categories of endorsement, based on the level of clinical confidence regarding the recommendation, as indicated by a bracketed Roman numeral after the statement. The three categories are as follows:

[I]   Recommended with substantial clinical confidence.
[II] Recommended with moderate clinical confidence.
[III] May be recommended on the basis of individual circumstances.

► B. GENERAL TREATMENT PRINCIPLES

Individuals with substance use disorders are heterogeneous with regard to a number of clinically important features and domains of functioning. Consequently, a multimodal approach to treatment is typically required. Care of individuals with substance use disorders includes conducting a complete assessment, treating intoxication and withdrawal syndromes when necessary, addressing co-occurring psychiatric and general medical conditions, and developing and implementing an overall treatment plan. The goals of treatment include the achievement of abstinence or reduction in the use and effects of substances, reduction in the frequency and severity of relapse to substance use, and improvement in psychological and social functioning.

1. Assessment

A comprehensive psychiatric evaluation is essential to guide the treatment of a patient with a substance use disorder [I]. The assessment includes 1) a detailed history of the patient's past and present substance use and the effects of substance use on the patient's cognitive, psychological, behavioral, and physiological functioning; 2) a general medical and psychiatric history and examination; 3) a history of psychiatric treatments and outcomes; 4) a family and social history; 5) screening of blood, breath, or urine for substance used; 6) other laboratory tests to help confirm the presence or absence of conditions that frequently co-occur with substance use disorders; and 7) with the patient's permission, contacting a significant other for additional information.

2. Psychiatric management

Psychiatric management is the foundation of treatment for patients with substance use disorders [I]. Psychiatric management has the following specific objectives: motivating the patient to change, establishing and maintaining a therapeutic alliance with the patient, assessing the patient's safety and clinical status, managing the patient's intoxication and withdrawal states, developing and facilitating the patient's adherence to a treatment plan, preventing the patient's relapse, educating the patient about substance use disorders, and reducing the morbidity and sequelae of substance use disorders. Psychiatric management is generally combined with specific treatments carried out in a collaborative manner with professionals of various disciplines at a variety of sites, including community-based agencies, clinics, hospitals, detoxification programs, and residential treatment facilities. Many patients benefit from involvement in self-help group meetings, and such involvement can be encouraged as part of psychiatric management.

3. Specific treatments

The specific pharmacological and psychosocial treatments reviewed below are generally applied in the context of programs that combine a number of different treatment modalities.

a) Pharmacological treatments

Pharmacological treatments are beneficial for selected patients with specific substance use disorders [I]. The categories of pharmacological treatments are 1) medications to treat intoxication and withdrawal states, 2) medications to decrease the reinforcing effects of abused substances, 3) agonist maintenance therapies, 4) antagonist therapies, 5) abstinence-promoting and relapse prevention therapies, and 6) medications to treat comorbid psychiatric conditions.

b) Psychosocial treatments

Psychosocial treatments are essential components of a comprehensive treatment program [I]. Evidence-based psychosocial treatments include cognitive-behavioral therapies (CBTs, e.g., relapse prevention, social skills training), motivational enhancement therapy (MET), behavioral therapies (e.g., community reinforcement, contingency management), 12-step facilitation (TSF), psychodynamic therapy/interpersonal therapy (IPT), self-help manuals, behavioral self-control, brief interventions, case management, and group, marital, and family therapies. There is evidence to support the efficacy of integrated treatment for patients with a co-occurring substance use and psychiatric disorder; such treatment includes blending psychosocial therapies used to treat specific substance use disorders with psychosocial treatment approaches for other psychiatric diagnoses (e.g., CBT for depression).

4. Formulation and implementation of a treatment plan

The goals of treatment and the specific therapies chosen to achieve these goals may vary among patients and even for the same patient at different phases of an illness [I]. Because many substance use disorders are chronic, patients usually require long-term treatment, although the intensity and specific components of treatment may vary over time [I]. The treatment plan includes the following components: 1) psychiatric management; 2) a strategy for achieving abstinence or reducing the effects or use of substances of abuse; 3) efforts to enhance ongoing adherence with the treatment program, prevent relapse, and improve functioning; and 4) additional treatments necessary for patients with a co-occurring mental illness or general medical condition.

The duration of treatment should be tailored to the individual patient's needs and may vary from a few months to several years [I]. It is important to intensify the monitoring for substance use during periods when the patient is at a high risk of relapsing, including during the early stages of treatment, times of transition to less intensive levels of care, and the first year after active treatment has ceased [I].

5. Treatment settings

Treatment settings vary with regard to the availability of specific treatment modalities, the degree of restricted access to substances that are likely to be abused, the availability of general medical and psychiatric care, and the overall milieu and treatment philosophy.

Patients should be treated in the least restrictive setting that is likely to be safe and effective [I]. Commonly available treatment settings include hospitals, residential treatment facilities, partial hospitalization programs, and outpatient programs. Decisions regarding the site of care should be based on the patient's ability to cooperate with and benefit from the treatment offered, refrain from illicit use of substances, and avoid high-risk behaviors as well as the patient's need for structure and support or particular treatments that may be available only in certain settings [I]. Patients move from one level of care to another based on these factors and an assessment of their ability to safely benefit from a different level of care [I].

Hospitalization is appropriate for patients who 1) have a substance overdose who cannot be safely treated in an outpatient or emergency department setting; 2) are at risk for severe or medically complicated withdrawal syndromes (e.g., history of delirium tremens, documented history of very heavy alcohol use and high tolerance); 3) have co-occurring general medical conditions that make ambulatory detoxification unsafe; 4) have a documented history of not engaging in or benefiting from treatment in a less intensive setting (e.g., residential, outpatient); 5) have a level of psychiatric comorbidity that would markedly impair their ability to participate in, adhere to, or benefit from treatment or have a co-occurring disorder that by itself would require hospital-level care (e.g., depression with suicidal thoughts, acute psychosis); 6) manifest substance use or other behaviors that constitute an acute danger to themselves or others; or 7) have not responded to or were unable to adhere to less intensive treatment efforts and have a substance use disorder(s) that endangers others or poses an ongoing threat to their physical and mental health [I].

Residential treatment is indicated for patients who do not meet the clinical criteria for hospitalization but whose lives and social interactions have come to focus predominantly on substance use, who lack sufficient social and vocational skills, and who lack substance-free social supports to maintain abstinence in an outpatient setting [II]. Residential treatment of ≥3 months is associated with better long-term outcomes in such patients [II]. For patients with an opioid use disorder, therapeutic communities have been found effective [II].

Partial hospitalization should be considered for patients who require intensive care but have a reasonable probability of refraining from illicit use of substances outside a restricted setting [II]. Partial hospitalization settings are frequently used for patients leaving hospitals or residential settings who remain at high risk for relapse. These include patients who are thought to lack sufficient motivation to continue in treatment, have severe psychiatric comorbidity and/or a history of relapse to substance use in the immediate posthospitalization or postresidential period, and are returning to a high-risk environment and have limited psychosocial supports for abstaining from substance use. Partial hospitalization programs are also indicated for patients who are doing poorly despite intensive outpatient treatment [II].

Outpatient treatment of substance use disorders is appropriate for patients whose clinical condition or environmental circumstances do not require a more intensive level of care [I]. As in other treatment settings, a comprehensive approach is optimal, using, where indicated, a variety of psychotherapeutic and pharmacological interventions along with behavioral monitoring [I]. Most treatment for patients with alcohol dependence or abuse can be successfully conducted outside the hospital (e.g., in outpatient or partial hospitalization settings) [II], although patients with alcohol withdrawal must be detoxified in a setting that provides frequent clinical assessment and any necessary treatments [I]. For many patients with a cocaine use disorder, clinical and research experience suggests the effectiveness of intensive outpatient treatment in which a variety of treatment modalities are simultaneously used and in which the focus is the maintenance of abstinence [II]. The treatment of patients with nicotine dependence or a marijuana use disorder occurs on an outpatient basis unless patients are hospitalized for other reasons [I].

6. Clinical features influencing treatment

In planning and implementing treatment, a clinician should consider several variables with regard to patients: comorbid psychiatric and general medical conditions, gender-related factors, age, social milieu and living environment, cultural factors, gay/lesbian/bisexual/transgender issues, and family characteristics [I]. Given the high prevalence of comorbidity of substance use disorders and other psychiatric disorders, the diagnostic distinction between substance use symptoms and those of other disorders should receive particular attention, and specific treatment of comorbid disorders should be provided [I]. In addition to pharmacotherapies specific to a patient's substance use disorder, various psychotherapies may also be indicated when a patient has a co-occurring psychiatric disorder, psychosocial stressors, or other life circumstances that exacerbate the substance use disorder or interfere with treatment [I]. A patient's cessation of substance use may also be associated with changes in his or her psychiatric symptoms or the metabolism of medications (e.g., altered antipsychotic metabolism via cytochrome P450 1A2 with smoking cessation) that will necessitate adjustment of psychotropic medication doses [I].

In women of childbearing age, the possibility of pregnancy needs to be considered [I]. Each of the substances discussed in this practice guideline has the potential to affect the fetus, and psychosocial treatment to encourage substance abstinence during pregnancy is recommended [I]. With some substances, concomitant agonist treatment may be preferable to continued substance use. In pregnant smokers, treatment with nicotine replacement therapy (NRT) may be helpful [II]. For pregnant women with an opioid use disorder, treatment with methadone [I] or buprenorphine [II] can be a useful adjunct to psychosocial treatment.

▶ C. NICOTINE USE DISORDERS: TREATMENT PRINCIPLES AND ALTERNATIVES

1. Pharmacological treatments

Pharmacological treatment is recommended for individuals who wish to stop smoking and have not achieved cessation without pharmacological agents or who prefer to use such agents [I]. There are six medications approved by the U.S. Food and Drug Administration (FDA) for nicotine dependence, including five NRTs (patch, gum, spray, lozenge, and inhaler) and bupropion. These are all first-line agents that are equally effective in alleviating withdrawal symptoms and reducing smoking. Any of these could be used based on patient preference, the route of administration, and the side-effect profile [I]. Significant adverse events to NRTs, including dependence, are rare. Although combined psychosocial and medication treatment produces the best outcomes in treating nicotine use disorders, these medications are effective even when no psychosocial treatment is provided [I]. Using a combination of these first-line treatments may also improve outcome [II]. Nortriptyline and clonidine have utility as second-line agents but appear to have more side effects [II]. Other medications and acupuncture have not been proven to be effective.

2. Psychosocial treatments

Psychosocial treatments are also effective for the treatment of nicotine dependence and include CBTs [I], behavioral therapies [I], brief interventions [II], and MET [II] provided in individual [I], group [I], or telephone [I] formats or via self-help materials [III] and Internet-based formats [III]. The efficacy of treatment is related to the amount of psychosocial treatment received. The 12-step programs, hypnosis, and inpatient therapy have not been proven effective.

D. ALCOHOL USE DISORDERS: TREATMENT PRINCIPLES AND ALTERNATIVES

1. Management of intoxication and withdrawal

The acutely intoxicated patient should be monitored and maintained in a safe environment [II]. Symptoms of alcohol withdrawal typically begin within 4–12 hours after cessation or reduction of alcohol use, peak in intensity during the second day of abstinence, and generally resolve within 4–5 days. Serious complications include seizures, hallucinations, and delirium.

The treatment of patients in moderate to severe withdrawal includes efforts to reduce central nervous system (CNS) irritability and restore physiological homeostasis [I] and generally requires the use of thiamine and fluids [I], benzodiazepines [I], and, in some patients, other medications such as anticonvulsants, clonidine, or antipsychotic agents [II]. Once clinical stability is achieved, the tapering of benzodiazepines and other medications should be carried out as necessary, and the patient should be observed for the reemergence of withdrawal symptoms and the emergence of signs and symptoms suggestive of co-occurring psychiatric disorders [I].

2. Pharmacological treatments

Specific pharmacotherapies for alcohol-dependent patients have well-established efficacy and moderate effectiveness. Naltrexone may attenuate some of the reinforcing effects of alcohol [I], although data on its long-term efficacy are limited. The use of long-acting, injectable naltrexone may promote adherence, but published research is limited and FDA approval is pending. Acamprosate, a γ-aminobutyric acid (GABA) analog that may decrease alcohol craving in abstinent individuals, may also be an effective adjunctive medication in motivated patients who are concomitantly receiving psychosocial treatment [I]. Disulfiram is an effective adjunct to a comprehensive treatment program for reliable, motivated patients whose drinking may be triggered by events that suddenly increase alcohol craving [II].

3. Psychosocial treatments

Psychosocial treatments found effective for some patients with an alcohol use disorder include MET [I], CBT [I], behavioral therapies [I], TSF [I], marital and family therapies [I], group therapies [II], and psychodynamic therapy/IPT [III]. Recommending that patients participate in self-help groups, such as Alcoholics Anonymous (AA), is often helpful [I].

E. MARIJUANA USE DISORDERS: TREATMENT PRINCIPLES AND ALTERNATIVES

Studies of treatment for marijuana use disorders are limited. No specific pharmacotherapies for marijuana withdrawal or dependence can be recommended [I]. In terms of psychosocial therapies, an intensive relapse prevention approach that combines motivational interventions with the development of coping skills may be effective for the treatment of marijuana dependence [III], but further study of these approaches is necessary.

F. COCAINE USE DISORDERS: TREATMENT PRINCIPLES AND ALTERNATIVES

1. Management of intoxication and withdrawal

Cocaine intoxication is usually self-limited and typically requires only supportive care [II]. However, hypertension, tachycardia, seizures, and persecutory delusions can occur with cocaine intoxication and may require specific treatment [II]. Acutely agitated patients may benefit from sedation with benzodiazepines [III].

2. Pharmacological treatments

Pharmacological treatment is not ordinarily indicated as an initial treatment for patients with cocaine dependence. In addition, no pharmacotherapies have FDA indications for the treatment of cocaine dependence. However, for individuals who fail to respond to psychosocial treatment alone, some medications (topiramate, disulfiram, or modafinil) may be promising when integrated into psychosocial treatments.

3. Psychosocial treatments

For many patients with a cocaine use disorder, psychosocial treatments focusing on abstinence are effective [I]. In particular, CBTs [I], behavioral therapies [I], and 12-step-oriented individual drug counseling [I] can be useful, although efficacy of these therapies varies across subgroups of patients. Recommending regular participation in a self-help group may improve the outcome for selected patients with a cocaine use disorder [III].

▶ G. OPIOID USE DISORDERS: TREATMENT PRINCIPLES AND ALTERNATIVES

1. Management of intoxication and withdrawal

Acute opioid intoxication of a mild to moderate degree usually does not require specific treatment [II]. However, severe opioid overdose, marked by respiratory depression, may be fatal and requires treatment in an emergency department or inpatient setting [I]. Naloxone will reverse respiratory depression and other manifestations of opioid overdose [I].

The treatment of opioid withdrawal is directed at safely ameliorating acute symptoms and facilitating the patient's entry into a long-term treatment program for opioid use disorders [I]. Strategies found to be effective include substitution of methadone or buprenorphine for the opioid followed by gradual tapering [I]; abrupt discontinuation of opioids, with the use of clonidine to suppress withdrawal symptoms [II]; and clonidine-naltrexone detoxification [II]. It is essential that the treating physician assess the patient for the presence of other substances, particularly alcohol, benzodiazepines, or other anxiolytic or sedative agents, because the concurrent use of or withdrawal from other substances can complicate the treatment of opioid withdrawal [I]. Anesthesia-assisted rapid opioid detoxification (AROD) is not recommended because of lack of proven efficacy and adverse risk-benefit ratios.

2. Pharmacological treatments

Maintenance treatment with methadone or buprenorphine is appropriate for patients with a prolonged history (>1 year) of opioid dependence [I]. The goals of treatment are to achieve a stable maintenance dose of opioid agonist and facilitate engagement in a comprehensive program of rehabilitation [I]. Maintenance treatment with naltrexone is an alternative strategy [I], although the utility of this strategy is often limited by lack of patient adherence and low treatment retention.

3. Psychosocial treatments

Psychosocial treatments are effective components of a comprehensive treatment plan for patients with an opioid use disorder [II]. Behavioral therapies (e.g., contingency management) [II], CBTs [II], psychodynamic psychotherapy [III], and group and family therapies [III] have been found to be effective for some patients with an opioid use disorder. Recommending regular participation in self-help groups may also be useful [III].

II. GENERAL TREATMENT PRINCIPLES

Although many of the principles presented in this section apply to all substances reviewed in this guideline (i.e., nicotine, alcohol, marijuana, cocaine, and opioids), not all principles are applicable to the treatment of every substance use disorder. This is particularly true for nicotine dependence treatment, as nicotine dependence rarely causes the behavioral or social harm seen with other substance dependencies.

Individuals with substance use disorders are heterogeneous with regard to a number of clinically important features:

- The number and type of substances used
- The individual's genetic vulnerability for developing a substance use disorder(s)
- The severity of the disorder, the rapidity with which it develops, and the degree of associated functional impairment(s)
- The individual's awareness of the substance use disorder as a problem
- The individual's readiness for change and motivation to enter into treatment for the purpose of change
- The associated general medical and psychiatric conditions (either co-occurring or induced by substance use)
- The individual's strengths (protective and resiliency factors) and vulnerabilities
- The social, environmental, and cultural context in which the individual lives and will be treated

It is clinically helpful when assessing patients to use a spectrum that includes *use, misuse, abuse,* and *dependence.* The latter two terms represent formal diagnostic categories. Use of a substance may or may not be clinically significant. If use of a substance is thought to be potentially clinically significant but does not meet diagnostic criteria for abuse or dependence, it may be characterized as "misuse," although this is not a formal diagnostic category. Even when functional impairment is absent or limited, substance misuse can be an early indicator of an individual's vulnerability to developing a chronic substance use disorder. Brief early interventions can effectively reduce this progression (1–3), although follow-up reinforcement appears necessary for sustained utility. Most individuals presenting or referred for treatment of a substance use disorder, however, have been unable to stop using substances on their own. They often exhibit functional impairments across many categories (e.g., health, social and family, occupational, financial, legal) and have a history of chronic or relapsing episodes of problematic substance use. This practice guideline refers primarily to the care of such individuals.

As with treatment models for chronic diseases, treatment for individuals with substance use disorders occurs in temporal phases that include initial assessment, acute intervention, and long-term intervention and/or maintenance, with frequent reassessment during episodic flares in substance use (4). During the assessment phase, the specific variables associated with an individual's substance use are evaluated (e.g., genetic vulnerability, environmental influences, behavioral patterns of use, positive and negative consequences of use, associated conditions that trigger or otherwise interact with use, risk of withdrawal). In addition, the level of risk for morbidity or mortality associated with substance use is determined. Immediate intervention to provide safety to the patient in a medically monitored environment is recommended for individuals who present with high-risk intoxication or withdrawal states or altered mental states (e.g., psychosis, suicidality, agitation) that are associated with a risk of danger to self or others. After the patient is stabilized, the patient's immediate needs regarding safety and stability should be addressed to prepare the patient to enter into comprehen-

sive, long-term treatment of the substance use disorder and its associated conditions. Such acute interventions may be focused on goals such as preserving health, achieving financial security, and finding stable housing. It is recommended that individuals in the patient's family or social network be included in the treatment process so they may learn about the disorder, help monitor the patient's progress, and assist in the patient's maintaining existing relationships or repairing troubled ones (5).

Depending on the clinical circumstances and an individual's readiness for change (6), treatment strategies may emphasize providing motivational enhancement, teaching risk-reduction behaviors and skills, helping the patient achieve abstinence and learn relapse prevention skills, or combining substitution agonist therapies (e.g., methadone or buprenorphine for opioid-dependent individuals, NRTs for tobacco-dependent individuals) with therapy to help the patient acquire relapse prevention skills. In addition, individuals with substance use disorders often require multimodal treatment to address associated conditions that have contributed to or resulted from the substance use disorder. Specific pharmacological and psychosocial treatments for patients with a substance use disorder are reviewed separately in this guideline; however, in practice they are often implemented together, as combined treatments lead to better treatment retention and outcomes (7).

▶ A. GOALS OF TREATMENT

The evidence to date suggests that substance-dependent individuals who achieve sustained abstinence from the abused substance have the best long-term outcomes (8, 9). Psychiatrists will, however, frequently encounter individuals who wish to reduce their substance use to a "controlled" level (i.e., use without apparent functional consequences). Although some of these individuals, particularly those with less severe problems, may be helped to reach a stable level of use (e.g., "controlled" drinking) that does not cause morbidity (10), a goal of "controlled" substance use is unrealistic for most individuals presenting with a substance use disorder. Furthermore, setting "controlled" use as a primary goal of treatment may initially dissuade individuals from working toward abstinence. However, treatment may be initially facilitated by the clinician's accepting the patient's goal for moderation while sharing with the patient any reservations the clinician may have about the likelihood of success. If the clinician believes that any level of substance use for the individual carries a risk of acute or chronic negative consequences, he or she should share with the patient this concern and the belief that long-term abstinence would be the best course of action. In certain circumstances it may be reasonable, however, for an individual to begin treatment by setting a short-term goal of reducing or containing dangerous substance use as a first step toward achieving the longer-term goal of sustained abstinence (11).

The goals for treating a substance use disorder begin with engaging the patient in treatment and may ultimately progress to the patient's achieving and maintaining complete abstinence from all problematic substances. Along this treatment spectrum or timeline, an individual and his or her physician may develop immediate goals involving risk reduction, such as reducing the frequency and quantity of substances taken, abstaining from some (but not all) substances according to assessment of risk (e.g., abstaining from injected heroin without abstaining from cannabis use), or limiting substance use to lower-risk situations (e.g., continuing to drink at home but avoiding drinking in other environments or driving while drinking). The guiding elements of treatment planning consist of ongoing efforts to reduce the patient's substance use and prevent a return to previously dangerous patterns of use. It is essential to complement this approach with parallel setting of goals to repair an individual's functional decline and develop new pathways for safe, sober pleasures. These issues are outlined below.

1. Treatment retention and substance use reduction or abstinence as initial goals of treatment

The ideal outcome for most individuals with substance use disorders is total cessation of substance use. Nonetheless, many individuals are either unable or unmotivated to reach this goal, particularly in the early phases of treatment and/or after a relapse to substance use. Such individuals can still be helped to minimize the direct and indirect negative effects of ongoing substance use. The interventions discussed in this practice guideline may result in substantial reductions in the general medical, psychiatric, interpersonal, familial/parental, occupational, or other difficulties commonly associated with substance abuse or dependence. For example, reductions in the amount or frequency of substance use, substitution of a less risky substance, and reduction of high-risk behaviors associated with substance use may be achievable goals when abstinence is initially unobtainable (12, 13). Engaging an individual to participate and remain in treatment that may eventually lead to further reductions in substance use and its associated morbidity is a critical early goal of treatment planning and is often enhanced by motivational interviewing techniques (14).

2. Reduction in the frequency and severity of substance use episodes

Reduction in the frequency and severity of substance use episodes is a primary goal of long-term treatment (15). The individual is educated about common types of substance use triggers, such as environmental cues, stress, and exposure to a priming substance (16, 17). The individual is then helped to develop skills to prevent substance use; these skills include identifying and avoiding high-risk situations as well as developing alternative responses to situations in which substance use may occur. Individuals are at a greater risk of using substances when any of the following are present: 1) craving or urges to use a substance due to acute or protracted withdrawal states and/or classically conditioned responses to cues associated with substance use (18–20); 2) easy access to substances; 3) social facilitation of substance use (e.g., holiday parties, association with other substance users); 4) negative affective states; 5) negative life events, or any significant, even positively viewed, life event if the event carries with it a significant increase in responsibility (e.g., marriage, the birth of a child, beginning school or a new job, work promotion); 6) physical discomfort; 7) unstructured time or boredom; or 8) nonadherence to prescribed treatment. Many clinicians do not recognize that individuals with substance use disorders have a chronic condition and may have future episodes of substance use. Therefore, the clinician may become discouraged when an individual doing well in treatment over an extended period of time resumes substance use. A useful clinical strategy is to explicitly anticipate the reality of future substance use and plan a strategy for recovery in the event of substance use relapse; such a strategy helps both the patient and the clinician optimally manage and contain the negative consequences resulting from a return to substance use.

3. Improvement in psychological, social, and adaptive functioning

Substance use disorders are associated with impairments in psychological development and social adjustment, family and social relations, school and work performance, financial status, health, and personal independence (e.g., as a result of legal charges associated with substance use, suspension of the individual's driver's license after being convicted of driving under the influence of an intoxicating substance) (21). For optimal outcome, the treatment of a substance use disorder may also include strategies that target repair of damages or losses that resulted from the individual's substance use; aid in developing effective interpersonal, vocational, and proactive coping skills; and enhance familial and interpersonal relations that will support an abstinent lifestyle. It is particularly important to provide comprehensive treatments when individuals have co-occurring psychiatric or general medical conditions that significantly influence relapse risk (e.g., chronic pain, depression, anxiety, impaired cognition, and impulse control disorders) (22–24).

TABLE 1. DSM-IV-TR Criteria for Substance Abuse

A. A maladaptive pattern of substance use leading to clinically significant impairment or distress, as manifested by one (or more) of the following, occurring within a 12-month period:

1) recurrent substance use resulting in a failure to fulfill major role obligations at work, school, or home (e.g., repeated absences or poor work performance related to substance use; substance-related absences, suspensions, or expulsions from school; neglect of children or household)

2) recurrent substance use in situations in which it is physically hazardous (e.g., driving an automobile or operating a machine when impaired by substance use)

3) recurrent substance-related legal problems (e.g., arrests for substance-related disorderly conduct)

4) continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance (e.g., arguments with spouse about consequences of intoxication, physical fights)

B. The symptoms have never met the criteria for substance dependence for this class of substance.

▶ B. ASSESSMENT

The term "substance use disorder" encompasses a number of different substances and disorders (i.e., abuse, dependence, intoxication, withdrawal, and psychiatric syndromes and disorders that result from substance use). Substance abuse and substance dependence are two disorders that are frequently encountered, and their criteria are applicable across substances. The criteria for these disorders are presented in Tables 1 and 2. However, it is beyond the scope of this practice guideline to describe all the substance use disorders, and the reader is referred to DSM-IV-TR for a full description.

A clinician's approach to assessing a substance use disorder will differ depending on the context in which an individual presents for treatment. An individual who recognizes the presence of a substance use disorder may present willingly for treatment and be amenable to a thorough assessment (as outlined below). However, many individuals will not be similarly motivated, and retaining them in treatment may require adapting the assessment process to their level of insight and motivational state. For example, individuals with benzodiazepine dependence will often present for treatment of an anxiety disorder but have no motivation to reduce their benzodiazepine use. Likewise, individuals with bipolar disorder will often present with a co-occurring substance use disorder but may not identify or recognize substance use as problematic (e.g., the use of alcohol at night to facilitate sleep onset). In such cases, educational efforts to help the individual recognize the substance use disorder as a problem may be helpful. This may involve extending the assessment phase over time rather than attempting to acquire all the patient's information at once so that the clinician can tailor the intervention to the patient's particular stage of change (25).

In an alternative scenario, an individual may be coerced into an assessment by frustrated family members or drug treatment diversion programs within the justice system. Such individuals may be resentful of the assessment process and have no motivation for changing their behavior other than the stipulations of family or the court system. Under these conditions, the clinician must attempt to establish an alliance with the individual in order to be viewed as a valuable source of information and aid rather than as a punitive extension of the referring sources. Retaining the individual in treatment will also take precedence over treating the disorder but may not always be possible. A full assessment of the individual's substance use disorder(s) may need to be gathered in pieces over time, with details being added to the initial picture when the individual is more comfortable sharing information pertinent to the pattern of his or her substance use and more motivated to contemplate change.

TABLE 2. DSM-IV-TR Criteria for Substance Dependence

A maladaptive pattern of substance use, leading to clinically significant impairment or distress, as manifested by three (or more) of the following, occurring at any time in the same 12-month period:

1) tolerance, as defined by either of the following:
   a) a need for markedly increased amounts of the substance to achieve intoxication or desired effect
   b) markedly diminished effect with continued use of the same amount of the substance

2) withdrawal, as manifested by either of the following:
   a) the characteristic withdrawal syndrome for the substance
   b) the same (or a closely related) substance is taken to relieve or avoid withdrawal symptoms

3) the substance is often taken in larger amounts or over a longer period than was intended

4) there is a persistent desire or unsuccessful efforts to cut down or control substance use

5) a great deal of time is spent in activities necessary to obtain the substance (e.g., visiting multiple doctors or driving long distances), use the substance (e.g., chain-smoking), or recover from its effects

6) important social, occupational, or recreational activities are given up or reduced because of substance use

7) the substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance (e.g., current cocaine use despite recognition of cocaine-induced depression, or continued drinking despite recognition that an ulcer was made worse by alcohol consumption)

The diagnosis should specify "With Physiological Dependence" (either item 1 or 2 is present) or "Without Physiological Dependence" (neither item 1 nor 2 is present).

All individuals undergoing a psychiatric evaluation should be screened for a substance use disorder, regardless of their age, presentation, or referral source. Several empirically validated screening tools are available that do not require extensive training or time to use during an initial assessment. Commonly used screens include the four-item CAGE screen for alcohol abuse (Have you ever felt the need to **C**ut down on drinking, been **A**nnoyed by others' criticism of your drinking, felt **G**uilty about drinking, needed an **E**ye-opener drink first thing in the morning?) (26), the 10-item Alcohol Use Disorders Identification Test (27), and the Drug Abuse Screening Test, a 20-item self-report assessment that screens for commonly abused substances other than alcohol (28). If screening instruments or other assessment questions reveal that an individual has ever used substances, it is important to obtain a history of current and past substance use, including the frequency of substance use and the quantity of the substance used per using episode. The clinician should also inquire about the individual's current caffeine and nicotine use, past cigarette use in pack-years (defined as the number of packs per day multiplied by the number of years of smoking), and, for current smokers, the time from waking in the morning to their first cigarette.

It is also important for the assessing clinician to inquire about specific substance misuse if an individual's work is associated with increased risk because of occupational demands, privileged access to controlled substances, or a desire to enhance performance. For example, firefighters, police, and emergency personnel have a high prevalence of alcohol dependence related to job stress (29). Misuse of prescription substances or anesthetics is common among health care or veterinary medicine personnel; when compared with other physicians who misuse substances, anesthesiologists have been shown to be more likely to misuse opioids (30). Synthesis and mis-

use of controlled substances have also been observed in medicinal chemists. Anabolic steroid hormone precursors may be misused by athletes, and stimulant drugs may be misused by commercial truck drivers attempting to stay awake longer or by models and actors wanting to lose weight. Cocaine use appears to be a hazard among staff in restaurants and the entertainment industry. The clinician will also want to ask about other situations in an individual's history that may put him or her at higher risk for substance misuse, such as a history of trauma, psychiatric disorders, or chronic medical conditions.

In evaluating an individual with a suspected or confirmed substance use disorder, a comprehensive psychiatric evaluation is essential. Information should be sought from the individual and, with the individual's consent, available family members and peers, current and past health professionals, employers, and others as appropriate. The goals of the assessment are to establish a multiaxial DSM-IV-TR diagnosis, including identification of current and past substance use disorders as well as other comorbid psychiatric and physical disorders, and to identify other factors that are important to developing a treatment plan. Specific elements of the assessment may include the following:

1. A systematic inquiry into the mode of onset, quantity, frequency, and duration of substance use; the escalation of use over time; the motivation for use; the specific circumstances of the individual's substance use (e.g., where, with whom, how much, by what route of administration); the desired effect of the substance used; the most recent dose of each substance used; the time elapsed since the most recent use; the degree of associated intoxication; the severity of associated withdrawal syndromes; and the subjective effects of all substances used, including substances other than the individual's "drug of choice." As the psychiatrist elicits the individual's substance use history, he or she should also determine if the individual meets DSM-IV-TR criteria for abuse or dependence (see Tables 1 and 2) for each substance used. Because many patients entering treatment for a specific substance use disorder are using more than one substance, assessment should routinely include questions about the use of multiple substances, including which substances are used in combination, in what order, and for what effect. Use of over-the-counter and prescription medications should also be ascertained. If prescription medications are being used, it is important to learn if the medication has been prescribed for the individual or for someone else.

2. A history of any prior treatment for a substance use disorder, including the characteristics of the treatment such as setting; context (e.g., voluntary or involuntary); modalities used; duration and, if applicable, dose of treatment; adherence to treatment; and short-term (3-month), intermediate (1-year), and longer-term outcomes as measured by subsequent substance use, level of social and occupational functioning achieved, and other outcome variables. Previous efforts to control or stop substance use outside of a formal treatment setting should also be discussed. For individuals who had previous treatment or periods of abstinence, additional history may include the duration of abstinence, the factors that promoted or helped sustain abstinence, the impact of abstinence on psychiatric functioning, the circumstances surrounding relapse (e.g., whether the relapse was related to withdrawal symptoms, exacerbation of a psychiatric disorder, or psychosocial stressors), the individual's attitude toward prior treatment, nontreatment experiences, and expectations about future treatments.

3. A comprehensive general medical and psychiatric history, including mental status and physical examination, to ascertain the presence or absence of co-occurring psychiatric or general medical disorders as well as signs and symptoms of intoxication or withdrawal. Psychological or neuropsychological testing may also be indicated for some individuals (e.g., to assess an individual's level of cognitive impairment). When a clinician is attempting to ascertain an individual's current medication use, he or she should specifically ask about prescribed and nonprescribed medications, including vitamins and herbal products.

4. Qualitative and quantitative blood and urine screening for substances of abuse and laboratory tests for abnormalities that may accompany acute or chronic substance use. These tests may also be used during treatment to monitor for potential relapse. For some substances, such as alcohol and nicotine, breath tests may also be useful.

5. Screening for infectious and other diseases often found in substance-dependent individuals (e.g., human immunodeficiency virus [HIV], tuberculosis, hepatitis). Such individuals, particularly those with evidence of compromised immune function, are at high risk for these diseases.

6. A complete family and social history, including information on familial substance use or other psychiatric disorders; social factors contributing to the development or perpetuation of the substance use disorder (e.g., social facilitation of substance use); financial or legal problems; social supports, including peer relationships; school or vocational adjustment; and other functional impairments. When obtaining the family and social history, the psychiatrist may also wish to ask for permission to speak to family members, friends, or other significant people in the individual's life who may be able to provide important information regarding the individual's substance use disorder. In evaluating the impact of the individual's current living environment on his or her ability to adhere to treatment and refrain from substance use, it is important to determine whether and how household members and friends have supported or interfered with prior attempts at abstinence. The substance use status of others in the household and close friends (e.g., never used substances, former substance user, current substance user) should also be considered. If others in the household are currently using substances, their willingness to quit at the same time as the individual or to refrain from substance use in the presence of the individual should be assessed.

7. Individual preferences, motivations, and barriers for treatment. Individuals vary in their treatment preferences regarding pharmacotherapy, group therapy, individual therapy, and self-help treatments. Working with the individual's preferences is likely to lead to better treatment adherence and outcomes (31). For individuals who have a co-occurring psychiatric disorder, exacerbation of psychiatric symptoms can be an additional barrier (31, 32).

When a clinician is assessing a new patient and establishing a diagnosis, it is often difficult to distinguish between psychiatric symptoms resulting from substance use and those from a co-occurring psychiatric disorder. Anxiety, depression, mania, and psychosis are all commonly induced by various substances and can be observed with chronic use as well as during specific substance-induced states, including intoxication and withdrawal. Evaluation of psychiatric symptoms in substance-using individuals can be enhanced with repeated, longitudinal psychiatric assessments. As part of the initial assessment, it may also be useful to draw a timeline of all substances used and all psychiatric symptoms and/or disorders and to include in this timeline all prior treatments. This timeline approach can help determine the chronology of symptom development (i.e., whether the signs and symptoms predate or follow the onset of repetitive substance use), the presence or absence of symptoms during extended substance-free periods (e.g., 3 months or more), and the impact of each disorder on the presentation, clinical course, and outcome of the other(s).

The probability that an individual with a substance use disorder has a co-occurring psychiatric disorder and not a substance-induced psychiatric disorder is increased if at least one first-degree relative has a documented history of a similar disorder, the individual's symptoms are not typically observed in conjunction with the use of a particular substance, there is a clear history that psychiatric symptoms preceded the onset of the substance use disorder, or the symptoms were evident during extended substance-free periods. Such a distinction is relevant when a clinician must decide whether to treat the psychiatric symptoms with medications and determine how long to maintain a medication once it is started. For example, individuals with certain substance-induced psychotic symptoms, such as paranoia resulting from the use of stimulants or

phencyclidine (PCP), may benefit from the short-term use of an antipsychotic medication. Conversely, symptoms of depression and anxiety coexisting with a substance use disorder may initially be addressed in psychosocial treatment but may require medication management if they do not improve over time.

▶ C. TREATMENT SETTINGS

Individuals with substance use disorders may receive care in a variety of settings. Treatment settings vary according to the availability of resources (e.g., the presence or absence of medical monitoring, the specialization of services and therapy provided, the availability of psychiatric consultation), the freedom allowed the individual (e.g., locked versus open unit), the intensity of treatment duration/participation, and the milieu philosophy driving the primary interventions (e.g., medical model, educational, 12-step, peer support, faith based). Because treatment best occurs in a system that encourages cessation of all harmful substance use (33), consideration should be given to making treatment sites smoke free (33, 34). Although most studies indicate that smoking cessation does not increase alcohol relapse and may aid recovery in substance-dependent patients (35–37), one study found that smoking cessation worsened drinking outcomes in a group of alcohol-dependent patients (38).

1. Factors affecting choice of treatment setting

Individuals should be treated in the least restrictive setting that is likely to prove safe and effective. Decisions regarding the site of care should be based on the individual's 1) capacity and willingness to cooperate with treatment; 2) ability for self-care; 3) social environment (which may be supportive or high risk); 4) need for structure, support, and supervision to remain safe and abstinent; 5) need for specific treatments for co-occurring general medical or psychiatric conditions; 6) need for particular treatments or an intensity of treatment that may be available only in certain settings; and 7) preference for a particular treatment setting. In addition, the choice of setting should be guided by the particular substance(s) used, the medical risks associated with use of the substance(s), the accessibility of appropriate levels of care, and the stated goals of the individual's treatment plan (as described in Sections III through VII and as determined by the individual's clinical status).

Patients should be moved from one level of care to another on the basis of these factors; the decision to move to a less intensive level of care should consider these factors plus the clinician's assessment of a patient's readiness and ability to benefit from the less restrictive setting. To appropriately match patients and treatment settings, many clinicians, health insurers, hospitals, and treatment agencies use the American Society of Addiction Medicine (ASAM) patient placement criteria (39). These criteria provide an algorithm for placement that represents expert consensus and that is updated as additional evidence becomes available on treatment outcomes and levels of care.

Studies comparing the short-term, intermediate, and long-term benefits of treatment in various settings (i.e., inpatient, residential, partial hospitalization, outpatient) have a variety of methodological problems, including heterogeneity of individual populations, high dropout rates, lack of controlled trials, inappropriate comparison of outcomes after time-limited treatment interventions, and reliance on individual self-reports uncorroborated by data from collateral sources (40). Stated treatment goals, program features, and outcome measures vary across studies (41). A common finding among different treatments available for substance use disorders is that retention in treatment improves outcomes (42–45).

2. Commonly available treatment settings and services

Settings and services used in the treatment of substance use disorders may be considered as points along a continuum of care from most to least intensive. The specific factors leading to

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the choice of a particular setting for an individual patient are described below. The choice of a treatment setting may also be influenced by availability, given that communities differ in the variety of treatment services they offer and certain specialized treatment settings (e.g., dual-diagnosis partial hospitalization care) may not be widely available. For individuals with primary nicotine dependence or marijuana use disorders, treatment occurs in outpatient settings; information presented about other treatment settings may not be applicable to these populations.

a) Hospitals

The range of services available in hospital-based programs typically includes emergency detoxification and stabilization during withdrawal; assessment and treatment of general medical and psychiatric conditions; group, individual, and family therapies; psychoeducation; motivational counseling; and social service facilitation of follow-up care in available community services (46, 47). Psychiatric hospitals may offer dual-diagnosis inpatient units that specialize in the stabilization of co-occurring psychiatric and substance use disorders. For patients admitted to hospital-level care for other reasons (general medical or psychiatric), smoking cessation programs may also be available.

Hospital-based treatment settings may be secure (i.e., locked) or may permit individuals and visitors to come and go in a monitored but generally less restrictive fashion. Secure hospital settings should be considered for individuals with co-occurring psychiatric conditions whose clinical state would ordinarily require such a unit (e.g., actively suicidal individuals). Individuals with poor impulse control and judgment who in the presence of an "open door" are likely to leave the program or obtain or receive drugs on the unit are also candidates for a secure unit. In some states, individuals can reside on a secure unit in "conditional voluntary" status, which requires written notice and a time delay (e.g., 3 days) before the patient's request for discharge is approved or another disposition (e.g., commitment) is implemented. Such restrictions can provide a useful period of delay in which poorly motivated individuals can reconsider their wish to leave a program prematurely.

The available data do not support the notion that hospitalization per se has specific benefits over other treatment settings beyond the ability to address treatment objectives that require a medically monitored environment (48, 49). There is consensus (e.g., ASAM patient placement criteria) that individuals in one or more of the following categories may require hospital-level care:

1. Individuals with drug overdoses who cannot be safely treated in an outpatient or emergency department setting (e.g., individuals with severe respiratory depression, individuals in a coma)
2. Individuals in withdrawal who are at risk for a severe or complicated withdrawal syndrome (e.g., individuals dependent on multiple substances, individuals with a history of delirium tremens) or cannot receive the necessary medical assessment, monitoring, and treatment in a less intensive setting
3. Individuals with acute or chronic general medical conditions that make detoxification in a residential or ambulatory setting unsafe (e.g., individuals with severe cardiac disease)
4. Individuals with a documented history of not engaging in or benefiting from treatment in a less intensive setting (e.g., residential, outpatient)
5. Individuals with marked psychiatric comorbidity who are an acute danger to themselves or others (e.g., individuals who have depression with suicidal thoughts, acute psychosis)
6. Individuals manifesting substance use or other behaviors who are an acute danger to themselves or others
7. Individuals who have not responded to less intensive treatment efforts and whose substance use disorder(s) poses an ongoing threat to their physical and mental health

In general, the duration of hospital-based treatment should be dictated by the individual's current need to receive treatment in a restrictive setting and his or her capacity to access, safely participate in, and benefit from treatment in a less restrictive setting.

b) Partial hospitalization programs and intensive outpatient programs

Partial hospitalization and intensive outpatient programs can provide an intensive, structured treatment experience for individuals with substance use disorders who require more services than those generally available in traditional outpatient settings. Although the terms "partial hospitalization," "day treatment," and "intensive outpatient" programs may be used nearly interchangeably in different parts of the country, the ASAM patient placement criteria (39) define structured programming in partial hospitalization programs as 20 hours per week and in intensive outpatient programs as 9 hours per week. Partial hospitalization programs provide ancillary medical and psychiatric services, whereas intensive outpatient programs may be more variable in the accessibility of these services. Some patients enter these programs directly from the community. Alternatively, these programs are sometimes used as "step-down" programs for individuals leaving hospital or residential settings who are at a high risk of relapsing because of problems with motivation, the presence of frequent cravings or urges to use a substance, poor social supports, immediate environmental cues for relapse and/or availability of substances, and co-occurring medical and/or psychiatric disorders. The goal of such a "step-down" approach is to stabilize patients by retaining them in treatment and providing more extended intensive outpatient monitoring of relapse potential and co-occurring disorders. Partial hospitalization and intensive outpatient programs may also be used as a brief "step-up" in treatment for an outpatient who has had a relapse but who does not require medical detoxification or who has entered into a high-risk period for relapse because of life circumstances or recurrence of a co-occurring medical and/or psychiatric symptom (e.g., depressed mood, increased pain).

The treatment components of partial hospitalization programs may include some combination of individual and group therapy, vocational and educational counseling, family meetings, medically supervised use of adjunctive medications (e.g., opioid antagonists, antidepressants), random urine screening for substances of abuse, and treatment for any co-occurring psychiatric disorders. Intensive outpatient programs use individual therapy, group therapy, family therapy, and urine toxicology but vary in the amount of other therapeutic components used (50). An advantage of intensive outpatient programs is the availability of evening programs that accommodate day-shift employees. The availability of weekend programs varies for both partial hospitalization and intensive outpatient programs. Both kinds of programs aim to prepare the individual for transition to less intensive outpatient services and increased self-reliance through the practice and mastery of relapse prevention skills and the active use of self-help programs.

Limited data are available for the efficacy of partial hospitalization and intensive outpatient programs. Randomized, controlled trials have demonstrated that some individuals who would ordinarily be referred for residential- or hospital-level care do just as well in partial hospitalization care (51, 52). One study (53) comparing a more time-intensive day hospital program to an intensive outpatient program that was actually less time intensive found no differences in outcome for cocaine-dependent individuals, and another study comparing intensive with traditional outpatient treatment of the same population found no differences in outcome (54).

c) Residential treatment

Residential treatment is indicated primarily for individuals who do not meet clinical criteria for hospitalization but whose lives and social interactions have come to focus exclusively on substance use and who currently lack sufficient motivation and/or substance-free social supports to remain abstinent in an ambulatory setting. For these individuals, residential facilities provide a safe and substance-free environment in which residents learn individual and group living skills for preventing relapse. As in the case of hospital-based programs, residential treatment pro-

grams frequently provide psychosocial, occupational, and family assessment; psychoeducation; an introduction to self-help groups; and referral for social or vocational rehabilitative services where necessary (55). Many residential programs provide their own individual, group, and vocational counseling programs but rely on affiliated partial hospitalization or outpatient programs to supply the psychosocial and psychopharmacological treatment components of their programs. Residential treatment settings should have access to general medical and psychiatric care that is required to meet individual needs.

The duration of residential treatment should be dictated by the length of time necessary for the patient to meet specific criteria that would predict his or her successful transition to a less structured, less restrictive treatment setting (e.g., outpatient care). These criteria may include a demonstrated motivation to continue in outpatient treatment, the ability to remain abstinent even in situations where substances are potentially available, the availability of a living situation and associated support system conducive to remaining substance free (e.g., family, substance-free peers), sufficient stabilization of any co-occurring general medical or psychiatric disorder so that the patient is considered suitable for outpatient aftercare, and the availability of adequate follow-up care.

In some areas, particularly urban centers, residential treatment programs specifically designed for adolescents, pregnant or postpartum women, or women with young children are available (56, 57).

d) Therapeutic communities

Individuals with opioid, cocaine, or multiple substance use disorders may benefit from referral to a long-term residential therapeutic community. These programs are generally reserved for individuals with a low likelihood of benefiting from outpatient treatment, such as individuals who have a history of multiple treatment failures or whose profound impairment in social relational skills or ability to attain and sustain employment impede adherence to outpatient treatment (58). Rather than viewing substance abuse as an illness (as defined by the disease concept), therapeutic community theory views it as a deviant behavior; that is, it is seen as a symptom of pathological development in personality structure, social relating, and educational and economic skills (reviewed by De Leon in reference 59). The therapeutic community milieu provides individual, social, and vocational rehabilitation through the community method of social learning. It is a highly structured, substance-free community setting in which the primary interventions are behavioral modeling, supportive peer confrontation, contingency management, community recreation, and work therapy designed to facilitate adherence to social norms and substance-free lifestyles (44).

Therapeutic communities are characteristically organized along strict hierarchies, with newcomers being assigned to the most menial social status and work tasks. Residents achieve higher status and take on increasing responsibility as they demonstrate that they can remain substance free and conform to community rules. Supportive confrontation, individually and in groups, is a primary intervention used to break through denial about the role of substance use in one's life, identify maladaptive behaviors and coping styles that lead to interpersonal conflict and vocational failure, suggest alternative ways of handling disturbing affects, and encourage the development of attitudes and beliefs that are incompatible with continued substance use.

Data regarding the effectiveness of traditional long-term (2-year commitment) therapeutic communities are limited by the fact that only 15%–25% of individuals admitted voluntarily complete a program, with maximum attrition occurring in the first 3 months (60, 61). Retention rates differ with program sites (62), and retention lengths predict outcomes on abstinence and lack of criminal recidivism indexes, with 2-year postcompletion success rates at 90% for graduates, 50% for dropouts completing >1 year, and 25% for dropouts completing <1 year (44, 63).

Cost-containment concerns and increasing knowledge of dual-diagnosis needs have led to modifications of the traditional therapeutic community model. Shorter-term programs (e.g., 3–12 months) and nonresidential programs are offered for those with fewer social and voca-

tional impairments. The expanded availability of social services has allowed improved treatment of special populations (e.g., dual-diagnosis, HIV-positive, single-parent, adolescent) in the therapeutic community setting, and some methadone maintenance programs are provided in this setting.

Potential voluntary applicants to a residential therapeutic community setting should have some understanding of the severity of their substance use disorder and a readiness to change their lifestyle; they should also have a willingness to conform to the structure of the therapeutic community and to temporarily sever ties with family and friends while they assimilate into the community environment. An individual's violation of community rules or shirking of work responsibilities is disclosed to all community members and may be grounds for discharge.

Therapeutic community settings have provided some of the better studied and more successful programs for treating incarcerated substance abusers (64). This has influenced the development of standardized staff training curricula (65).

e)   Community residential facilities

Community residential facilities are commonly known as "halfway houses" or "sober houses," with the former typically offering more structure and supervision. They provide an outpatient substance-free housing environment as a transitional setting for individuals in recovery who are not yet able to manage independent housing without a significant risk for relapse. Some studies have shown that for patients with multiple service needs (e.g., vocational, housing, transportation), the provision of stable housing in the form of long-term community residential facilities leads to significantly improved substance use outcomes (66–68). This benefit has been demonstrated for adult substance users of both sexes. Community residential facilities show more variability in substance use outcomes for youth and adolescents (69); this may be related to inadequate matching of services to individual needs.

f)   Aftercare

Aftercare occurs after an intense treatment intervention (e.g., hospital or partial hospitalization program) and generally includes outpatient care, involvement in self-help approaches, or both. The clinician should consider the possibility that cognitive impairment may be present in recently detoxified patients when determining their next level of care. Research on aftercare has examined different treatment models, including eclectic, medically oriented, motivational, 12-step, cognitive-behavioral, group, and marital strategies (see Section II.F). Given the chronic, relapsing nature of many types of substance use disorders, especially those requiring hospitalization, it is expected that aftercare will be recommended with few exceptions. In fact, if addiction is reconceptualized along the lines of a chronic rather than an acute disease model, as recommended by McLellan et al. (4), the distinction between a "treatment episode" and "aftercare" should be removed and the different modalities of care (e.g., inpatient, outpatient) be reconsidered as part of a continuous, long-term treatment plan.

g)   Outpatient settings

Outpatient treatment settings include but are not limited to mental health clinics, integrated dual-diagnosis programs, private practice settings, primary care clinics, and substance abuse treatment centers, including opioid treatment programs. For individuals with primary nicotine dependence or a marijuana use disorder, treatment is always provided in an outpatient setting. For individuals with other substance use disorders, outpatient treatment is appropriate when clinical conditions or environmental and social circumstances do not require a more intensive level of care.

As in other treatment settings, the optimal outpatient approach is a comprehensive one that includes a variety of psychotherapeutic and pharmacological interventions along with behavioral monitoring, where indicated. The evidence base for empirically supported outpatient

treatments is larger for alcohol, nicotine, and opioid dependence treatments than for other substance dependence treatments (70–74). In addition to medication therapies (see Section II.E), outpatient treatments with strong evidence of effectiveness include CBTs (e.g., relapse prevention, social skills training), MET, behavioral therapies (e.g., community reinforcement, contingency management), TSF, psychodynamic therapies/IPT, self-help manuals, behavioral self-control, brief interventions, case management, and group, marital, and family therapies (see Section II.F).

Many specific outpatient treatments have been designed to enhance an individual's participation in treatment and sense of self-efficacy regarding the reduction or cessation of problematic substance use. As in the case of residential and partial hospitalization programs, high rates of attrition can be problematic in outpatient settings, particularly in the early phase (i.e., the first 6 months). Because intermediate and long-term outcomes are highly correlated with retention in treatment, individuals should be strongly encouraged to remain in treatment (42, 43, 45). Clinicians should also encourage and attempt to integrate into treatment a patient's participation in self-help programs where appropriate (see Section II.F.9) (75).

h) Case management

Case management, by definition, exists as an adjunctive treatment. The goals of case management interventions are to provide advocacy and coordination of care and social services and to improve patient adherence to prescribed treatment and follow-up care (76). Case management initially provides psychoeducation about the patient's diagnosis and treatment as well as assessment and stabilization of basic necessities required for the individual to actively participate in treatment (e.g., housing, utilities, income, health insurance, transportation). Beyond this, case managers aid individuals in maintaining stability and understanding and adhering to prescribed treatment. The variability in case management models has complicated research on the effectiveness of this approach (77, 78). Nevertheless, studies show that case management interventions are effective for individuals with an alcohol use disorder (79) or co-occurring psychiatric and substance use disorders (80) and for adolescents with substance use disorders (81).

i) Legally mandated treatment

Treatment of substance use disorders may be legally mandated under a variety of circumstances, including substance-related criminal offenses such as driving under the influence of alcohol or drugs. Drug court programs recognize the effectiveness of diverting offenders with lesser drug-related convictions from correctional facilities into court-mandated community programs for the treatment of substance use disorders (82). Standard procedures for drug court programs include 1) assessment of individual substance use treatment needs, 2) appropriate referral for treatment after arrest, 3) periodic monitoring of adherence to treatment through the use of clinician report and mandatory drug testing, 4) reduction in the severity of charges contingent on successful utilization of programs for the treatment of substance use disorders, and 5) aftercare planning for maintaining sobriety in the community. For offenses related to driving under the influence of alcohol or drugs, state and community sanctions include incarceration, license suspension, driver's education, and community service requirements. Some evidence indicates that more severe sanctions lead to less recidivism for intoxicated drivers with high blood alcohol content readings (83).

Despite the high frequency at which substance use disorders and criminal behaviors co-occur, it has been estimated that only 1%–20% of substance abusers receive adequate treatment while incarcerated (84). The most studied effective treatment programs for incarcerated individuals are therapeutic communities (see Section II.C.2.d) (64).

j) Employee assistance programs

Employee assistance programs (EAPs) provide an employment-based treatment setting and referral platform for employees with substance use disorders. EAPs differ according to workplace

size and location. A critical difference for substance use treatment received through an EAP versus through an alternate community outpatient setting is the definition of successful intervention outcome. Whereas most community settings define successful outcome as a reduction of substance use and related medical and social problems, an EAP defines and measures success primarily through job performance. This reflects the employer's need to serve and retain an employee while simultaneously protecting the workplace from inadequate job performance and attributable losses (85). EAPs are cost-effective in the short term (86, 87), but posttreatment follow-up rates are poor (88).

▶ D. PSYCHIATRIC MANAGEMENT

Successful treatment of substance use disorders may involve the use of multiple specific treatments, the choice of which may vary for any one individual over time, and may involve clinicians from a variety of backgrounds. Psychiatric management entails the ongoing process of choosing from among various treatments, monitoring patients' clinical status, and coordinating different treatment components. The frequency, intensity, and focus of psychiatric management must be tailored to meet each patient's needs, and the type of management is likely to vary over time, depending on the patient's clinical status.

1. Motivating change

In recent years, there has been a great deal of research and clinical emphasis on the clinician's role in motivating patients with substance use disorders to change their behaviors. Motivational interviewing techniques (49) were developed specifically for the treatment of patients with a substance use disorder. These involve the use of an empathic, nonjudgmental, and supportive approach to examining the patient's ambivalence about changing addictive behaviors. Understanding the patient's stage of readiness to change (precontemplation, contemplation, preparation, action, or maintenance stage) (25) allows the clinician to determine what motivational strategies are most appropriate for the patient at that time. One of the goals of motivational interviewing is to elicit the patient's reasons for change and assist the patient in moving through the subsequent stages of change (89).

Other techniques involved in motivating change include A-FRAMES (see Section II.F.10) and METs. Manuals describing these techniques are available (49, 90).

2. Establishing and maintaining a therapeutic framework and alliance

An essential feature of psychiatric management of patients with a substance use disorder is the establishment and maintenance of a therapeutic alliance wherein the psychiatrist empathically obtains the necessary diagnostic and treatment-related information, gains the confidence of the patient and perhaps significant others, and is available in times of crisis. The frequency and duration of treatment contacts should be sufficient to engage the patient and, where appropriate, significant others in a sustained effort to participate in all relevant treatment modalities and, where appropriate, self-help groups. Within the context of this alliance, the primary goal of treatment is to help the patient learn, practice, and internalize changes in attitudes and behaviors that are conducive to relapse prevention (91, 92). The strength of the therapeutic alliance has been found to be a significant predictor of psychotherapy outcome (93). For example, several studies of individuals with substance use disorders have found that a stronger patient-clinician alliance predicts less substance use and better psychological functioning by the patient (94–96), although one of these studies found no association between therapeutic alliance strength and treatment retention for patients enrolled in a methadone maintenance program (96). Despite the finding of this one study, the chronic and relapsing nature of substance use disorders highlights the importance of establishing a therapeutic relationship so that patients

will return for additional treatment, if necessary (33, 97–99). Ackerman and Hilsenroth (100) reviewed therapist attributes and strategies that facilitate a positive therapeutic alliance for all patient populations. They found that being flexible, honest, respectful, confident, warm, and open all contributed to the development of a positive therapeutic alliance. The most effective strategies for developing such an alliance included exploration, reflection, highlighting past therapy successes, providing accurate interpretation, facilitating the expression of affect, and attending to the patient's experience.

A review of the literature on effective characteristics of therapists concluded that the characteristic most associated with patient retention and reduced substance use is strong interpersonal skills (101). Safran and Muran (102) reviewed techniques for repairing ruptures in the therapeutic alliance, such as clarifying misunderstandings, helping patients learn that they can express their needs in an individuated fashion and assert themselves without destroying the therapeutic relationship, and changing the tasks and goals to be more relevant to the patient's current needs. Limit setting has an important role in treatment of substance use disorders and may be particularly important for individuals with co-occurring personality disorders (103, 104).

3. Assessing safety and clinical status

The psychiatric assessment establishes a diagnosis and provides a baseline determination of a patient's clinical status. Ongoing evaluation of the patient's safety is also critical, as the patient's clinical status may change over time. It is particularly important to assess patients for suicidal or homicidal thoughts or other dangerous behavior—such as driving while under the influence of substances, domestic violence, or child abuse or neglect—that may need to be addressed through a change in the treatment plan or care setting.

Because relapse to substance use is common and inconsistently reported by patients (particularly when use is met with negative consequences or a judgmental response), breath, blood, saliva, and urine testing are helpful in the early detection of relapse. These tests are often initially conducted on a frequent and random schedule, as many substances and their metabolites may be detected for only a few days after use. Random urine screening for recent (i.e., within the last 1–3 days) substance use may be supplemented by nonrandom testing when recent substance use is suspected.

Methods of urine screening vary as to levels of sensitivity, specificity, and cost. The psychiatrist should be familiar with the applicability and sensitivity of the available analytic methods and collection procedures used in local laboratories, and he or she should specify the suspected type of substance used when requesting testing. Direct supervision of a patient's voiding or the use of other procedures (e.g., temperature-sensitive cups) will help to increase the validity and reliability of the test results.

The decision to test a patient's breath, blood, or urine depends on the type of substance use suspected, the substance's duration of action, the sensitivity of the test used, and the clinical setting in which care is being rendered. For example, blood testing is useful for assessing very recent substance use because it reflects current blood levels, and breath testing is useful for detecting alcohol intoxication and generally gives results comparable to those from blood tests. However, breath testing for alcohol is frequently preferred because the results are immediate and it is a noninvasive and low-cost procedure. Breath testing can also detect carbon monoxide, an indicator of smoking, as recent as a few hours before the test (105).

Urine testing is useful for detecting substance use over the preceding 5-day period for common substances of abuse (cocaine, opiates, cannabis, amphetamines, benzodiazepines, and PCP); however, certain opioids (buprenorphine, oxycodone, hydrocodone, and fentanyl) cannot be detected with routine methods and require special assays. Alcohol can be detected for up to 24 hours in urine, whereas ethyl glucuronide (EtG), a minor metabolite of alcohol, can be detected in the urine for 2–3 days after alcohol ingestion (106–108). Because EtG is pro-

duced by in vivo metabolism of alcohol prior to excretion in urine, the assay for EtG is highly sensitive and specific and is sometimes used in monitoring programs. Finally, there is some evidence that certain state markers can be used to detect recent alcohol use (e.g., elevation of carbohydrate-deficient transferrin, mean corpuscular volume, or γ-glutamyl transpeptidase).

Results from some studies have indicated that more intensive monitoring of substance use may increase recovery rates from a substance use disorder, as has been demonstrated with physicians and pilots (109–111). Ongoing assessment of the substance use disorder and psychiatric status is also necessary to ensure that the patient is receiving the appropriate treatment(s) and to monitor the patient's response to treatment (i.e., to determine the optimal dose of a medication, evaluate its efficacy, and detect treatment-emergent side effects). Co-occurring psychiatric disorders may complicate the treatment of the substance use disorder (111) and require the addition of specific treatments (e.g., an antidepressant medication for a patient with co-occurring major depressive disorder). An ongoing longitudinal assessment of the patient may be critical to the accurate diagnosis of a co-occurring condition (see Section II.B).

4. Managing intoxication

In general, acutely intoxicated patients require a safe, monitored environment in which they can receive decreased exposure to external stimulation, as well as reassurance, reorientation, and reality testing. Clinical assessment involves ascertaining which substances have been used; the route of administration, dose, and time since the last dose; whether the level of intoxication is waxing or waning; and other diagnostic information, as has been already described. Management of acute intoxication may also be directed toward hastening the removal of substances from the body, which may be accomplished through gastric lavage (in the case of substances that have been recently ingested) or techniques that increase the excretion rate of substances or their active metabolites. Medications that antagonize the actions of the abused substances may be used to reverse their effect. Examples include the administration of naloxone to patients who have overdosed with heroin or other opioids or flumazenil to patients who have overdosed with benzodiazepines.

Many patients use multiple substances simultaneously to enhance, ameliorate, or otherwise modify the degree or nature of their intoxication or to relieve withdrawal symptoms. Intoxication with alcohol and cocaine, the use of heroin and cocaine ("speedball"), and the combined use of alcohol, marijuana, and/or benzodiazepines by opioid-dependent patients are particularly frequent. When intoxication with multiple substances is present, the effects of each substance need to be taken into consideration in managing the patient. More information on the management of alcohol, cocaine, and opioid intoxication can be found in the specific section for each substance (Sections IV.C.1, VI.C.1, and VII.C.2, respectively).

5. Managing withdrawal

Not all individuals who are intoxicated or using substances will develop withdrawal symptoms. Withdrawal syndromes usually occur in physically dependent individuals who discontinue or reduce their substance use after a period of heavy and regular use. Patients using multiple substances (including alcohol and nicotine) are at risk for withdrawal from each substance. Factors that predict the severity of a withdrawal syndrome include 1) type of substance used, 2) time elapsed since last use, 3) metabolic rates of the substance, 4) dissociation rates of the substance from receptor sites, 5) synergistic effects or drug-drug interactions from the concomitant use of other prescribed or nonprescribed medications, 6) the presence or absence of concurrent general medical or psychiatric disorders, and 7) past withdrawal experiences (especially for alcohol). More information on the management of withdrawal from alcohol, cocaine, and opioids can be found in the specific section for each substance (Sections IV.C.2, VI.C.2, and VII.C.3, respectively).

6. Reducing the morbidity and sequelae of substance use disorders

The clinician should engage the patient and, when appropriate, significant others in developing a comprehensive treatment plan to address problems in biological, psychological, and social functioning. Coordination with a patient's primary care physician may also be important in the medical management of patients with substance use disorders (112).

Substance use disorders are commonly associated with substance-related medical morbidity. Although an individual patient's presentation may warrant specific screening and intervention, a number of baseline screening tests are frequently recommended based on epidemiological studies documenting the high risk for co-occurring medical disorders. For example, electrolyte panels and complete blood counts may be considered for those with severe substance dependence of any type because of the high correlation of substance dependence with poor nutritional status. For women of childbearing age, testing for pregnancy is an important part of medical screening. Tuberculin skin testing may be appropriate because of substance users' increased risk for tuberculosis exposure and to address public health concerns. Blood pressure monitoring may be advisable for substance users because of associated hypertension (e.g., with alcohol, nicotine, and stimulants) and hypotension (e.g., dehydration associated with poor self-care) risks. For individuals with specific substance use disorders, additional laboratory and other screening tests may be considered. These include the following:

- *Alcohol use.* Hepatic panel to screen for liver toxicity and functioning; complete blood count to determine mean corpuscular volume, which can be increased with hepatic toxicity, thiamine, folate, and vitamin B_{12} deficiency, as well as the direct effects of alcohol on hematopoiesis; stool sampling for occult blood reflecting gastritis, peptic ulcerative disease, or esophageal varices; mental status examination to detect cognitive functioning deficits
- *Nicotine dependence.* Examination of lymph nodes, mouth, and throat to assess for occult cancer and pulmonary disease; auscultation of chest and lungs; chest X-ray; pulmonary function testing, if warranted; electrocardiogram because of increased risk for cardiovascular disease; urine or blood cotinine level
- *Injection drug use.* Blood testing for blood-borne and sexually transmitted diseases, such as HIV, hepatitis B and C virus, and syphilis; skin examination for cellulitis; complete blood count to detect occult infection; genital examination and sampling for chlamydia, gonococcal disease, and human papilloma virus

Even if not initially caused by substance use, co-occurring medical disorders may be exacerbated by substance use, such as respiratory disease worsened by nicotine use; cardiovascular disease worsened by cocaine, alcohol, or nicotine use; hepatic disease aggravated by alcohol abuse; and seizure disorder exacerbated by withdrawal from alcohol, benzodiazepines, or other sedatives. In addition, individuals with substance use disorders frequently neglect preventive health care and follow-up medical care (113). All substance use disorders can be a cause for nonadherence to prescribed medications. Delayed dosing, missed dosing, or overuse of prescribed medications may occur during intoxication and withdrawal states. To finance substance use, individuals may sell prescribed medications (e.g., opiate analgesics) or avoid filling prescriptions to save insurance copayments. "Downward drift" and homelessness among substance-dependent individuals also often curtails their access to medical and dental care.

Individuals with a co-occurring psychiatric disorder are particularly vulnerable to the self-neglect and morbidity associated with substance use, possibly resulting in exacerbation of depression and suicidal thinking, worsening of psychosis, destabilization of bipolar disorder, and increased impulsivity leading to high-risk behaviors. Nonadherence to prescribed medication occurs frequently in those with a substance use disorder and further exacerbates these sequelae. Such individuals are best served by being referred to an integrated psychiatric and substance

use disorder treatment program (114). Psychiatrists are often the only medical contacts for patients with co-occurring psychiatric and substance use disorders and therefore are important resources for the facilitation of appropriate medical screening, referral for medical care, and follow-up with medical care (115).

7. Facilitating adherence to a treatment plan and preventing relapse

Because individuals with substance use disorders are often ambivalent about giving up their substance use, it can be useful to monitor their attitudes about participating in treatment and adhering to specific recommendations. These patients often deny or minimize the negative consequences attributable to their substance use; this tendency is often erroneously interpreted by clinicians and significant others as evidence of dishonesty. Even patients entering treatment with high motivation to achieve abstinence will struggle with the reemergence of craving for a substance or preoccupation with thoughts about attaining or using a substance. Moreover, social influences (e.g., substance-using family or friends), economic influences (e.g., unemployment), medical conditions (e.g., chronic pain, fatigue), and psychological influences (e.g., hopelessness, despair) may make an individual more vulnerable to a relapse episode even when he or she adheres to prescribed treatment. For these reasons, it can be helpful for clinicians and patients to anticipate the possibility that the patient may return to substance use and to agree on a corrective plan of action should this occur. If the patient is willing, it can be helpful to involve significant others in preventing the patient's relapse and prepare significant others to manage relapses should they occur.

Supporting patients in their efforts to reduce or abstain from substance use positively reinforces their progress. Overt recognition of patient efforts and successes helps to motivate patients to remain in treatment despite setbacks. Clinicians can optimize patient engagement and retention in treatment through the use of motivational enhancement strategies (49, 116) and by encouraging patients to actively partake in self-help strategies. Monitoring programs, such as EAPs and impaired-physician programs (86, 111, 117), can sometimes help patients adhere to treatment.

Early in treatment a clinician may educate patients about cue-, stress-, and substance-induced relapse triggers (17, 118). Patients benefit from being educated in a supportive manner about relapse risk situations, thoughts, or emotions; they must learn to recognize these as triggers for relapse and learn to manage unavoidable triggers without resorting to substance-using behaviors. Participation in AA or similar self-help group meetings can also support patients' sobriety and help them avoid relapse. Many other strategies can also help prevent relapse. Social skills training is targeted at improving individual responsibility within family relationships, work-related interactions, and social relationships. During the early recovery phase, it can be helpful to encourage patients to seek new experiences and roles consistent with a substance-free existence (e.g., greater involvement in vocational, social, or religious activities) and to discourage them from instituting major life changes that might increase the risk of relapse. Facilitating treatment of co-occurring psychiatric and medical conditions that significantly interact with substance relapse is a long-term intervention for maintaining sobriety (119–121).

Therapeutic strategies to prevent relapse have been well studied and include teaching individuals to anticipate and avoid substance-related cues (e.g., assessing individual capacity to avoid relapse in the presence of substance-using peers), training individuals how to monitor their affective or cognitive states associated with increased craving and substance use, behavioral contingency contracting, training individuals in cue extinction and relaxation therapies to reduce the potency of substance-related stimuli and modulate craving intensity, and supporting patients in the development of coping skills and lifestyle changes that support sobriety (122, 123). Behavioral techniques that enhance the availability and perceived value of social reinforcement as an alternative to substance use or reward for remaining abstinent have also been used (124).

If relapse does occur, individuals should be praised for even limited success and encouraged to continue in or resume treatment. Clinicians may help patients analyze relapses as well as periods of sobriety from a functional and behavioral standpoint and use what is learned to adjust the treatment plan to fit the individual's present needs. For chronically relapsing substance users, medication therapies may be necessary adjuncts to treatment.

8. Providing education about substance use disorders and their treatment

Patients with substance use disorders should receive education and feedback about their disorder, prognosis, and treatment. Clinicians are responsible for educating patients and their significant others about the etiology and nature of substance use, the benefits of abstinence, the risk of switching addictions (e.g., to other substances, to addictive behaviors such as compulsive gambling), the identification of relapse triggers, the availability of treatment options, and the role of family and friends in aiding or impeding recovery. When appropriate, psychiatrists may provide education about the effects of alcohol and other substances on the brain, the positive changes that occur with abstinence, substance-related medical problems (e.g., hepatitis C virus), and the effects of smoking, alcohol, and other substances on fetal development. Education on reducing behavioral harm may include advice about the use of sterile needles, procedures for safer sex, contraceptive options, and the availability of treatment services for drug-exposed newborns. Patients may also be directed to other educational resources. For example, public health services for the treatment of nicotine dependence are offered free of charge and are available by telephone (e.g., the "telephone quitlines" for individual states sponsored by the Centers for Disease Control and Prevention [CDC], available at http://www.cdc.gov/tobacco/quitlines.htm), on the Internet (e.g., the CDC's Tobacco Information and Prevention Source, available at http://www.cdc.gov/tobacco/), and by mail. As in all clinical settings, patient education is best delivered with due consideration to the individual's educational background and cultural setting.

9. Facilitating access to services and coordinating resources among mental health, general medical, and other service systems

In all aspects of patient management, the psychiatrist may work collaboratively with members of other professional disciplines, community-based agencies, treatment programs, and lay organizations to coordinate and integrate the patient's care and address the patient's social, vocational, educational, and rehabilitative needs. This is particularly important for patients lacking resources or the capacity for self-care because of a psychiatric or medical disorder. Case management services are aimed at such coordination of care (125).

In treating an individual with significant comorbidities or treatment-resistant disorders (e.g., chronic pain syndromes, personality disorders, cognitive impairment, chronic suicidality), it may be important for the treating clinician to consult with colleagues and experts in specialty care. In some cases, it may be necessary to place patients in a highly supervised setting to protect them and society from their dangerous behaviors associated with substance use.

▶ E. SOMATIC TREATMENTS

Medication therapies for substance use disorders are effective adjuncts to behavioral therapies and self-help groups; the settings for medication therapies include hospitals, partial hospitalization and intensive outpatient programs, and a variety of outpatient settings including primary care clinics, mental health clinics, substance use disorder treatment facilities, and private practice offices.

The types of accepted and effective medication strategies used in the treatment of specific substance use disorders are discussed in greater detail in later sections of this practice guideline. The following sections describe the general principles of these main categories of medication interventions: 1) medications to treat intoxication states, 2) medications to treat withdrawal syndromes,

3) agonist maintenance therapies, 4) antagonist therapies, 5) abstinence-promoting and relapse prevention therapies, and 6) medications to treat co-occurring psychiatric conditions.

1. Medications to treat intoxication states

Most clinicians treating patients with substance use disorders do not direct medical treatment of life-threatening intoxication states, because this role belongs to trained emergency physicians. However, clinicians who treat patients with substance use disorders should be able to recognize potentially dangerous intoxication states so they can make a rapid referral to emergency services. This section briefly describes potentially dangerous states of substance intoxication and emergency medication therapies.

In general, there are two types of medication interventions for acute intoxication and overdose: the administration of specific antagonists (e.g., naloxone for acute opioid overdose, flumazenil for acute benzodiazepine overdose complicated by ingestion of multiple substances) and therapies that stabilize the physical effects of substance overdose (e.g., anticholinergics, adrenergic pressor agents, anti-arrhythmics, anticonvulsants). Other adjunctive supportive treatments for overdose include establishing an adequate airway, decreasing the risk of aspiration (e.g., positioning the patient on his or her side, use of a cuffed endotracheal tube), and, if indicated, providing ventilatory support and hemodialysis. Hemodialysis or lavage therapies may also be used to enhance elimination of ingested substances.

The syndrome of acute opioid overdose is recognizable by respiratory depression, extreme miosis, and stupor or coma (126). Pulmonary edema may also be observed. Naloxone is a competitive antagonist at all three types of opiate receptors (mu, kappa, and sigma) and has no intrinsic agonist activity (127). It is clinically indicated to rapidly reverse a known or suspected opioid overdose (126, 128). Because of its poor bioavailability from significant hepatic first-pass effects, naloxone is typically administered intravenously, but it may also be given intramuscularly, subcutaneously, or endotracheally if intravenous access is unattainable (126). The dosing of naloxone varies depending on whether the patient is known to be opioid dependent as well as on the extent of respiratory depression. For example, in patients with CNS but not respiratory depression, an initial dose of 0.05–0.4 mg i.v. is recommended. The lower dose is used for opioid-dependent individuals, who will show withdrawal symptoms within minutes of being given the medication (129). For any person who presents with significant respiratory depression, the initial suggested dose is 2.0 mg i.v., regardless of the individual's drug use history; a beneficial response should occur within 2 minutes. Repeated doses can be administered every 3 minutes until respiratory or CNS depression is completely reversed or until a maximum dose of 10 mg i.v. has been given (128). If no response is observed after administration of the 10 mg of naloxone, the diagnosis of opioid overdose should be reconsidered. Because naloxone is rapidly absorbed by the brain and then quickly redistributed and eliminated from the body, its activity in the brain is short-lived (126, 130). Thus, further monitoring and infusion of additional naloxone are needed to continue antagonizing the effects of severe opioid overdose, particularly if longer-acting opioids have been ingested (128, 131). Monitoring for opioid withdrawal symptoms is also indicated because patients may experience significant distress that can last for several hours after reversal of an opioid overdose with an antagonist (129).

Acute sedative-hypnotic overdose is recognizable by slurred speech, loss of coordination, and confusion and, in a severe overdose, stupor, respiratory depression, and coma. Flumazenil is a potent benzodiazepine-specific antagonist that competes at central synaptic GABA receptor sites in a dose-dependent manner (132). In addition, it may antagonize the sedative effects of other compounds that act through GABA receptors, such as zolpidem, zaleplon, and eszopiclone (133). However, it does not antagonize benzodiazepine effects at peripheral GABAergic (e.g., renal, cardiac) receptor sites (134). Like naloxone, flumazenil has poor bioavailability and a brief duration of activity and is administered by repeated boluses or through continuous intravenous infusion. Although it can be used as a low-dose (2 mg i.v.) diagnostic probe for sus-

pected benzodiazepine overdose or in the reversal of benzodiazepines given for diagnostic or therapeutic procedures, flumazenil must be carefully administered to benzodiazepine-dependent patients and patients who have ingested mixed substances to avoid the production of withdrawal seizures (135). Flumazenil can also affect cerebral hemodynamics and is not recommended for situations in which intracranial pressure may already be increased (e.g., in the case of a head injury) (135). For these reasons, as well as cost, flumazenil is not recommended for uncomplicated benzodiazepine overdose that can be successfully managed by supportive ventilation therapies.

2. Medications to treat withdrawal syndromes

Patients who develop tolerance to a particular substance also develop cross-tolerance to other substances in the same pharmacological class. Physicians can take advantage of cross-tolerance in the treatment of withdrawal states by replacing the abused substance with a medication that is in the same pharmacological class. Examples of this include the use of methadone or buprenorphine in the treatment of opioid withdrawal, benzodiazepines in the treatment of alcohol and sedative-hypnotic withdrawal, and NRTs in the treatment of nicotine dependence (136–141).

Other medications are used to ameliorate indirect withdrawal-related symptoms. For example, clonidine is an α_2-adrenergic agonist that is useful in treating opioid withdrawal symptoms as well as anxiety syndromes (129, 142). Nonspecific symptoms of withdrawal such as headache and stomach upset may also require treatment using medications such as acetaminophen and histamine$_2$-receptor antagonists, respectively.

3. Agonist maintenance therapies

Opioid agonist maintenance therapy may be the primary tool available to engage an opioid-dependent individual in treatment because it relieves unpleasant withdrawal syndromes and craving associated with abstinence. The central and subjective effects of agonist therapies render these agents more acceptable to opioid-dependent patients than antagonist therapies, and adherence with treatment with agonist therapies is greater than with antagonist therapies.

Opioid agonist maintenance therapies (described further below) include methadone, a long-acting potent agonist at the mu opiate receptor sites (126), and buprenorphine, a potent long-acting compound that acts as a partial opioid agonist at mu receptor sites (126) and that is prescribed alone or with naloxone (in a combination tablet). An additional opioid agonist therapy, L-α-acetylmethadol (LAAM), has an extended duration of action and high intrinsic activity at the mu opiate receptor, but it has been withdrawn from the U.S. market by its manufacturer because of the risk of cardiac arrhythmia.

4. Antagonist therapies

Antagonist therapies are used to block or otherwise counteract the physiological and/or subjective reinforcing effects of substances. The narcotic antagonist naltrexone blocks the subjective and physiological effects of subsequently administered opioid drugs (e.g., heroin) (143, 144) without tolerance developing to its antagonist effect (145) (see Sections VII.C.1.c and IX.E.1.b). Compared with naloxone, naltrexone has good oral bioavailability (126) and a relatively long half-life; it is also available in a long-acting injectable preparation that may improve treatment adherence.

Mecamylamine, a nicotine antagonist, has also been studied, but its effectiveness remains unclear (146, 147).

5. Abstinence-promoting and relapse prevention therapies

For promoting abstinence and preventing relapse in patients with substance use disorders, certain medications may be useful. Examples of such medications are disulfiram, naltrexone, and acamprosate for alcohol use disorders and bupropion for nicotine dependence.

The ingestion of alcohol after disulfiram, an inhibitor of the enzyme aldehyde dehydrogenase, has been taken results in the accumulation of toxic levels of acetaldehyde accompanied by a host of unpleasant, potentially dangerous but rarely lethal signs and symptoms (148–151). The purpose of disulfiram is not to make the patient ill but to prevent the patient from drinking impulsively because he or she knows the symptoms that will result from drinking while taking disulfiram (see Sections IV.C.3.b and IX.B.3.b).

Naltrexone, described above as an antagonist therapy for the treatment of opiate dependence, is also effective in reducing alcohol craving and preventing alcohol-induced relapse (152–154), presumably because of the effect of mu opiate receptor antagonism in blocking the centrally mediated reinforcing effects of alcohol (155) (see Sections IV.C.3.a and IX.B.3.a).

Acamprosate (calcium bis-acetyl homotaurine) is a small, flexible molecule that resembles GABA and decreases glutamatergic neurotransmission, perhaps by acting as an N-methyl-D-aspartate antagonist (151, 156). It has been proposed that this medication helps sustain abstinence in detoxified alcohol-dependent individuals by reducing neuronal hyperexcitability during early recovery (156, 157) (see Sections IV.C.3.c and IX.B.3.c).

Treatment of nicotine dependence with the sustained-release formulation of the antidepressant bupropion has been associated with reductions in nicotine craving and smoking urges (158–160). The mechanism of action for bupropion in the treatment of nicotine dependence is unclear but is likely related to blockade of dopamine and norepinephrine reuptake (161) as well as antagonism of high-affinity nicotinic acetylcholine receptors (162) (see Sections III.E.2 and IX.A.1.b).

6. Medications to treat co-occurring psychiatric conditions

The treatment of co-occurring psychiatric disorders may or may not improve treatment outcome for the substance use disorder, but if treatment of the co-occurring psychiatric disorder does not occur, it is less likely that the treatment of substance use disorder will be successful. The high prevalence of co-occurring psychiatric disorders in substance-dependent patients implies that many such patients will require specific pharmacotherapy for a co-occurring disorder. Examples include the use of mood stabilizers for substance-dependent patients with bipolar disorder, antipsychotics for patients with psychotic disorders, and antidepressants for patients with major depressive disorder (see also Section II.G.2.d).

Clinically significant issues for substance-dependent patients receiving pharmacotherapy for co-occurring psychiatric disorders include 1) synergy of prescribed medications and effects of the abused substance (e.g., benzodiazepines and alcohol), 2) drug-drug interactions that affect the efficacy of psychiatric treatment (e.g., antipsychotics and smoked tobacco), 3) nonadherence to treatment because of intoxication and withdrawal states as well as drug-seeking behaviors, and 4) intentional or unintentional overdose. Certain medications used to treat co-occurring psychiatric disorders may themselves be abused. For example, patients with a co-occurring anxiety disorder may abuse benzodiazepines, patients with attention deficit hyperactivity disorder (ADHD) may abuse prescribed stimulants, and patients with a co-occurring psychotic disorder who are treated with anticholinergics for antipsychotic adverse side effects may abuse the anticholinergic adjunct. Substance-dependent patients may also misuse prescribed medications in an attempt to ameliorate withdrawal syndromes, enhance the effect of other substances of abuse, or accelerate the action of the prescribed medication. Whenever possible, medications with low abuse potential and relative safety in overdose should be selected for the treatment of patients with a co-occurring substance use disorder.

▶ F. PSYCHOSOCIAL TREATMENTS

Some type of psychosocial intervention is usually available in specialized substance use disorder treatment programs. These approaches are the mainstay of treatment for users of certain classes

of substances (e.g., cocaine) for which there are no pharmacological treatments with established efficacy. The major psychotherapeutic treatments that have been studied in patients with substance use disorders are cognitive-behavioral, behavioral, psychodynamic/interpersonal, and recovery-oriented therapies. A growing body of efficacy data from controlled clinical trials suggests that psychotherapy is superior to control conditions as a treatment for patients with a substance use disorder. However, no particular type of psychotherapy has been found to be consistently superior when compared with other active psychotherapies for treating substance use disorders. Even comparatively brief psychotherapies appear to have durable effects among patients with a substance use disorder (123).

After a discussion of the role of psychotherapy in substance abuse treatment and the relation between psychotherapy and pharmacotherapy, this section reviews the major psychosocial treatment approaches, the principles underlying their use, and their application in the treatment of patients with substance use disorders.

1.   Role of psychosocial treatments

Psychosocial treatments for substance use disorders attempt to counteract compulsive substance use by bringing about changes in patients' behaviors, thought processes, affect regulation, and social functioning. Although the techniques and theories of therapeutic action vary widely across the different approaches reviewed below, they all address one or more of a set of common tasks: 1) enhancing motivation to stop or reduce substance use, 2) teaching coping skills, 3) changing reinforcement contingencies, 4) fostering management of painful affects, and 5) enhancing social supports and interpersonal functioning (163). A central challenge for clinicians treating individuals with substance use disorders is that the core symptom, compulsive substance use, at least initially results in euphoria or relief of dysphoria, with the aversive and painful effects of substance use occurring some time after the rewarding effects. This contrasts with the course of most other psychiatric disorders (e.g., mood or anxiety disorders), in which the primary symptoms are painful or aversive. In addition, substance use has come to serve an important function in the individual's life by the time treatment is sought. Sustained recovery from a substance use disorder entails both relinquishing a valued element of life and developing different behaviors, thought patterns, and relationships that serve the functions previously met by substance use (164).

Psychosocial treatments are often essential for many aspects of this recovery process: Sustained motivation is required to forgo the rewards of substance use, tolerate the discomforts of early and protracted withdrawal symptoms, and gather the energy to avoid relapse despite episodes of craving that can occur throughout a lifetime. Coping skills are required to manage and avoid situations that place the individual at high risk for relapse. Alternative sources of reward or symptom relief must be sought and used to fill the place of substance use. Dysphoric affects, such as anger, sadness, or anxiety, must be managed in ways that do not involve continued substance use. Social relationships that are supportive of recovery need to be developed or repaired.

Patients with substance use disorders vary widely in their need for attention to each of these aspects of recovery, and brief treatment or self-help methods may be sufficient for the recovery of highly motivated patients with good interpersonal functioning and social support. However, none of these processes can be assumed to occur simply as a result of detoxification or with the administration of medications. It is essential that these psychosocial aspects of recovery be evaluated during treatment planning to determine the need for behavioral treatments.

2.   Relation of psychosocial treatments to pharmacotherapy for substance use disorders

Research has demonstrated that the utility of pharmacotherapies for substance use disorders may be limited unless they are delivered with adjunctive psychotherapy. For example, naltrexone maintenance for opioid dependence is plagued by high rates of premature dropout (165,

166) that can be lessened by concurrent behavioral or family therapy (167). Without adjunctive psychotherapy, the utility of disulfiram may be limited, in part because of low rates of medication adherence (150); however, its effectiveness can be enhanced when it is delivered in the context of a contract with a family member or significant other (168). Methadone maintenance for opioid dependence is the most successful pharmacological treatment of a substance use disorder, with substantial evidence of its impact on treatment retention and associated reductions in opioid use and illegal activity (169). However, cross-program effectiveness varies widely in relation to the quality and amount of ancillary psychosocial services delivered (169). Moreover, McLellan et al. (170) have shown that methadone maintenance alone yields acceptable results for only a small fraction of patients and that outcome is enhanced in proportion to the intensity of concomitant psychosocial services. More recently, a meta-analysis confirmed that a combination of psychosocial treatment and methadone maintenance produced greater reductions in heroin use by opioid-dependent individuals than methadone maintenance alone (171). Similar results have been found with nicotine replacement treatments: rates of sustained abstinence are increased two- to fourfold when they are combined with behavioral therapies (172, 173).

These findings suggest that even the most efficacious pharmacotherapies for substance use disorders have limitations that need to be addressed with psychosocial interventions. First, medications frequently affect only part of the substance dependence syndrome while leaving other aspects untouched. For example, methadone is highly effective in relieving withdrawal symptoms and minimizing the impact of continued opioid use, but by itself it has limited impact on counteracting social impairments resulting from protracted substance use prior to a patient's entering treatment (169). Also, most medications have variable or partial effects on the target symptom. Second, side effects or delayed effects of medications may limit acceptability and adherence. Third, medications typically target only one class of substances, whereas abuse of multiple substances is the norm in treatment populations (174). Fourth, gains made while taking the medication tend to diminish when the treatment is discontinued, whereas vulnerability to relapse is lifelong. Psychosocial strategies for countering these limitations and enhancing effectiveness of pharmacotherapies include 1) increasing a patient's motivation to stop substance use by taking the prescribed medication, 2) providing guidance to the patient on using the medication and managing its side effects, 3) maintaining the patient's motivation to continue the medication after an initial period of abstinence is achieved, 4) providing the patient with a supportive therapeutic relationship aimed at preventing premature termination, and 5) helping the patient develop skills to adjust to a life without substance use.

The importance of psychosocial treatments is reinforced by the recognition that there are only a handful of effective pharmacotherapies for substance use disorders and that, for the most part, these therapies are limited to the treatment of opioid, alcohol, and nicotine dependence (175). Effective pharmacotherapies for dependence on cocaine and other stimulants, marijuana, hallucinogens, and sedative-hypnotics have yet to be developed. For individuals who abuse these latter substances, psychosocial therapies remain the principal treatments.

Although the foregoing discussion has emphasized the need for psychotherapy to enhance the effectiveness of pharmacotherapy, this section would not be complete without considering the role of pharmacotherapy in enhancing the efficacy of psychotherapy. These two treatments have different mechanisms of action and targeted effects that can counteract the weaknesses of either treatment alone. Psychotherapies effect change by psychological means in the psychosocial aspects of substance abuse, such as motivation, coping skills, dysfunctional thoughts, or social relationships. The weaknesses of these treatments include a limited effect on the physiological aspects of substance abuse or withdrawal. Also, the impact of behavioral treatments tends to be delayed, requiring practice, repeated sessions, and a "working through" process. In contrast, the relative strength of pharmacological treatments is their rapid action in reducing immediate or protracted withdrawal symptoms, craving, and the rewarding effects of continued substance use. In effect, pharmacotherapies for substance use disorders reduce the patients' immediate ac-

cess to and preoccupation with the abused substance, freeing the patient to address other concerns such as long-term goals or interpersonal relationships. When medications are used in conjunction with psychotherapy, the dropout rate from therapy is reduced because the patient's urges to use and relapse to substance use are alleviated by the effects of the medication. In addition, a longer duration of abstinence can further enhance the efficacy of psychotherapy by preventing substance-related effects on attention and mental acuity, thereby maximizing the patient's ability for learning new behaviors in therapy.

Because of the complementary actions of psychotherapies and pharmacotherapies, combined treatment has a number of potential advantages. As is reviewed later, research evidence on combined treatment is sparse but generally supportive. Although factors such as patient acceptance can limit the use of combined approaches, it is important to note that for the treatment of substance use disorders, no studies have shown that combined treatments are less effective than either psychotherapy or pharmacotherapy alone.

3. Cognitive-behavioral therapies

CBTs for the treatment of substance use disorders are based on social learning theories regarding the acquisition and maintenance of the disorder (176). These therapies target two processes conceptualized as underlying substance abuse: 1) dysfunctional thoughts, such as the belief that the use of substances is completely uncontrollable, and 2) maladaptive behaviors, such as acceptance of offers to use drugs. Early versions of this approach (177, 178) were derived from cognitive therapy for depression and anxiety by Beck and Emery (179) and placed primary emphasis on identifying and modifying dysfunctional thinking patterns. Other adaptations of this approach have broadened the focus of therapy to help the patient master an individualized set of coping strategies as an effective alternative to substance use (176, 180). Typical cognitive strategies include fostering the patient's resolve to stop using substances by exploring positive and negative consequences of continued use, recognizing seemingly irrelevant decisions that could culminate in high-risk situations, and identifying and confronting thoughts about substance use. Behavioral strategies are based on a functional analysis of substance use (i.e, understanding substance use in relation to its antecedents and consequences) and include the development of strategies for coping with craving, preparing for emergencies, and coping with relapse to substance use.

Social skills training, an element of CBT, recognizes that alcohol and drug dependence commonly results in the interruption of normal developmental acquisition of social skills as well as the deterioration of previously learned social skills because of the interference of drug-seeking and drug-using behaviors. Social skills training targets an individual's capacity for 1) effective and meaningful communication, 2) listening, 3) being able to imagine someone else's feelings and thoughts to inform one's own behavioral interactions, 4) being able to monitor and modify one's own nonverbal communications, 5) being able to adapt to circumstances to maintain relationships, and 6) being assertive (181). This strategy has been successfully used as an adjunct to a more comprehensive treatment plan and can be delivered in a wide variety of outpatient treatment settings. It may be particularly useful in certain dually diagnosed populations, such as patients with schizophrenia (182) and adolescents at risk for beginning substance abuse (183).

Relapse prevention is a treatment approach in which CBT techniques are used to help patients develop greater self-control to avoid relapse (184, 185). Specific relapse prevention strategies include discussing the patient's ambivalence about the substance use disorder, identifying emotional and environmental triggers of craving and substance use, developing and reviewing specific coping strategies to deal with internal or external stressors, exploring the decision chain leading to reinitiation of substance use, learning from brief episodes of relapse (slips) about triggers leading to relapse, and developing effective techniques for early intervention (184, 186). In more recent clinical trials (43, 187), techniques drawn from cognitive therapy and relapse prevention have been combined with the aims of initiating abstinence and preventing relapse.

4. Motivational enhancement therapy

MET is the longer-term follow-up to an initial brief intervention strategy. It continues the use of motivational interviewing and moves a patient closer to a readiness to change substance use behaviors (reviewed in DiClemente et al. [6] and Miller and Rollnick [49]). It combines techniques from cognitive, client-centered, systems, and social-psychological persuasion approaches and may be provided by trained clinicians in substance abuse facilities, mental health clinics, and private practice offices. MET is characterized by an empathic approach in which the therapist helps to motivate the patient by asking about the pros and cons of specific behaviors, exploring the patient's goals and associated ambivalence about reaching those goals, and listening reflectively to the patient's responses. This treatment modality is effective even for patients who are not highly motivated to change, which gives it a practical advantage over other therapies for substance use disorders in many settings.

5. Behavioral therapies

Behavioral therapies are based on basic principles of learning theory (188), which deals with the role of externally applied positive or negative contingencies on learning or unlearning of behaviors that can range from simple autonomic reactions such as salivation to complex behavioral routines such as purchasing drugs. When these theories are applied to substance use disorders, the target behavior is habitual excessive substance use, which is altered through systematic environmental manipulations that vary widely depending on the specific substance use behavior. These theories differ from those underlying CBTs by not recognizing cognition as a domain independent of behavior.

The shared goals of behavioral therapies are to interrupt the sequence of substance use in response to internal or external cues and substitute behaviors that take the place of or are incompatible with substance use. There are two broad classes of learning theory-based treatments: 1) those that are based on classical conditioning and focus more on antecedent stimuli such as cue exposure therapy (189) and 2) those that are based on operant conditioning and focus more on consequences such as community reinforcement therapy (190). Representative behavioral approaches are briefly described here.

a) Contingency management

Contingency management therapy involves introducing rewards for therapeutically desired behaviors (e.g., attending therapy sessions, providing substance-negative urine samples) and/or aversive consequences for undesirable behaviors (e.g., failure to adhere to clinic rules) (191–193). As an adjunctive treatment, contingency management has been used with a variety of substances of abuse, including cocaine (193–196), opiates (197–200), and marijuana (201). Incentives to be offered, behaviors to be reinforced, and the reinforcement schedule vary widely by substance and also depend on the role of contingency management within the larger treatment plan (188). Although most studies have centered on abstinence from substance use, contingency management procedures are potentially applicable to a wide range of target behaviors and problems, including treatment retention, adherence to treatment (e.g., retroviral therapies for individuals with HIV), and reinforcement of other treatment goals such as employment seeking (202) or work attendance (203). Contingency management is effective when desired behaviors are rewarded with vouchers that can be exchanged for mutually agreed-on items such as movie tickets. Other reinforcers (e.g., free housing, direct compensation) can be substituted for vouchers. The use of large but low-probability reinforcers (e.g., earning the chance to draw from a bowl and win prizes of varying magnitudes ranging from $1 to more than $100) is also effective (204, 205) and may reduce the total costs of contingency management approaches (206).

Contingency contracting is a subtype of contingency management based on the use of predetermined positive or negative consequences to reward abstinence or punish, and thus deter, drug-related behaviors. Negative consequences of substance use may include notification of

courts, employers, or family members. The effectiveness of this approach depends heavily on the concurrent use of frequent, random, supervised urine screening for substance use. When negative contingencies are based on the anticipated response of others (e.g., spouses, employers), the treating physician should obtain the patient's written informed consent to contact these individuals at the time the contract is initiated (207).

b) Community reinforcement

The community reinforcement approach (CRA) is based on the theory that environmental reinforcers for substance use perpetuate substance use disorders and that, at the same time, patients with substance use disorders lack positive environmental reinforcers for sober activities and pleasures (208). CRA aims to provide individuals with substance use disorders with natural alternative reinforcers by rewarding their involvement in the family and social community; thus, family members or peers play a role in reinforcing behaviors that demonstrate or facilitate abstinence (190). In CRA, emphasis is placed on improving environmental contingencies for activities of a sober lifestyle to make that type of lifestyle preferable to a substance-dependent lifestyle. In addition to individual behavioral treatment and contingency management, the multifaceted CRA treatment package typically includes conjoint marital therapy, training in finding a job, counseling on substance-free social and recreational activities, and a substance-free social club. CRA is often applied with contingency management incentives (e.g., vouchers for recreation or food) that are used to reward evidence of sober behavior (209, 210). CRA has been shown to be effective in treating alcohol dependence, with adjunctive disulfiram treatment increasing its effectiveness (211). CRA can be clinic or office based, but it is largely practiced in residential or partial hospitalization programs, therapeutic communities, and community residential facilities.

c) Cue exposure and relaxation training

Cue exposure treatment involves exposing a patient to cues that induce craving while preventing actual substance use and, therefore, the experience of substance-related reinforcement (212). Cue exposure can also be paired with relaxation techniques and drug-refusal training to facilitate the extinction of classically conditioned craving (213, 214). As an alternative, relaxation training has been used alone to provide a nonsubstance response to counteract dysphoric affects or anxiety.

d) Aversion therapy

Aversion therapy involves coupling substance use with an unpleasant experience such as mild electric shock, pharmacologically induced vomiting, or exaggerated effects of the substance. This treatment seeks to eliminate substance use behaviors by pairing them with punishment.

6. Psychodynamic and interpersonal therapies

Psychodynamic psychotherapies vary but generally attribute symptom formation and personality characteristics to traumas and deficits during an individual's development that result in unconscious psychological conflict, faulty learning, and distortions of intrapsychic structures as well as internal object relations (215) and that have a profound effect on interpersonal relationships. These developmental events and their sequelae are inextricably interconnected to the individual's underlying neurobiology (as determined by genetic and other influences), which can in turn be altered by life experience, including learning, psychological events, and psychotherapy (216). Systematic testing of the efficacy of psychodynamic treatments for substance use disorders has occurred only with supportive-expressive therapy (217), a comparatively brief psychodynamically oriented treatment based on the use of interpretation and a supportive therapeutic relationship to modify negative views of the self and others. Two trials have supported the efficacy of supportive-expressive therapy for methadone-maintained, opioid-dependent pa-

tients (177, 218). However, an additional randomized trial found that combined individual and group drug counseling was superior to a combination of individual support-expressive therapy and group drug counseling in treating patients with cocaine dependence (219).

IPT for substance use disorders is based on the concept that dysfunctional social relationships either cause or prevent recovery from a substance use disorder (220). By discovering the relation between interpersonal problems and substance use, the patient can move toward making changes aimed at building a social network that is supportive of recovery. Clinical study of IPT for substance use disorders has been limited.

7. Group therapy

Group therapy is viewed as an integral and valuable part of the treatment regimen for many patients with a substance use disorder. Many different types of therapies have been used in a group format with this population, including CBT, IPT, and behavioral marital, modified psychodynamic, interactive, rational emotive, Gestalt, and psychodrama therapies (221–225).

Group therapies permit efficient use of therapist time (226). In addition, aspects of group therapy may make this modality more effective than individual treatment for individuals with a substance use disorder. For example, given the social stigma attached to having lost control of substance use, the presence of other group members who acknowledge having a similar problem can provide comfort. In addition, other group members who are further along in their recovery can act as models, illustrating that attempts to stop substance use are not futile. These more experienced group members can offer a wide variety of coping strategies that go beyond the repertoire known even by the most skilled individual therapist. Furthermore, group members frequently can act as "buddies" who offer continued support outside of group sessions in a way that most professional therapists do not.

Finally, the public nature of group therapy provides a powerful incentive to individuals to avoid relapse. The ability to publicly declare the number of days sober coupled with the fear of having to publicly admit to relapse is a strong force that helps group members fight a disorder that is characterized by a breakdown of internalized control mechanisms. Individuals with substance use disorders have been characterized as having poorly functioning internal self-control mechanisms (227, 228), and the group process can provide a robust source of external control. Moreover, because the group is composed of individuals recovering from substance use disorders, members may be better at detecting each other's concealed substance use or early relapse signals than would an individual therapist who may not have personal experience with a substance use disorder.

Although clinical trials of group therapy for substance use disorders are comparatively rare, the available data suggest that the efficacy of group treatment is comparable with that of individual therapies (229, 230). No compelling empirical evidence is available to document the advantages or disadvantages of choosing group or individual treatment for substance use disorders. Because many patients have experience with group or individual therapy, patient preferences should be considered when choosing between the two types of treatment delivery or when developing a combined treatment program.

8. Family therapies

Dysfunctional families, characterized by impaired communication among family members and an inability of family members to set appropriate limits or maintain standards of behavior, are associated with poor short- and long-term treatment outcome for patients with substance use disorders (231). Family therapy may be delivered in a formal, ongoing therapeutic relationship or through periodic contact. Goals of family therapy include obtaining information about the patient's current attitudes toward substance use, treatment adherence, social and vocational adjustment, level of contact with substance-using peers, and degree of abstinence, as well as encouraging family support for abstinence, maintaining marital and family relationships, and

improving treatment adherence and long-term outcome (232–235). They may also include behavioral contracting to maintain treatment (e.g., contracting with a partner for disulfiram treatment) or increasing positive incentives associated with sober family activities. Even the brief involvement of family members in the treatment program can enhance treatment engagement and retention.

Controlled studies have shown positive outcomes of involving non-alcohol-abusing family members in the treatment of an alcohol-abusing individual (236). More recent studies have demonstrated the effectiveness of family involvement in substance use disorder treatment for both women and men (237, 238), including patients on methadone maintenance (170). Family therapy, often in combination with other approaches, has also been studied extensively and has shown good evidence for efficacy in adolescents (239–242).

Different theoretical orientations of family therapy include structural, strategic, psychodynamic, systems, and behavioral approaches. Family interventions include those focused on the nuclear family; on the patient and his or her spouse or partner; on concurrent treatment for patients, spouses or partners, and siblings; on multifamily groups; and on social networks (120, 243, 244). Of the many types of family therapy used to treat substance use disorders, the preponderance of clinical trial evidence has been obtained for the behavioral and strategic approaches (245). The support for behavioral couples treatment is particularly strong (246).

Family intervention is indicated in circumstances in which a patient's abstinence upsets a previously well-established but maladaptive style of family interaction (233, 247) and in which other family members need help adjusting to a new set of individual and family goals, attitudes, and behaviors. Family therapy that addresses interpersonal and family interactions leading to conflict or enabling behaviors can reduce the risk of relapse for patients with high levels of family involvement. A major role for family and couples intervention is to enlist concerned significant others to foster treatment seeking and retention in family members who are unmotivated to change substance abuse behaviors. As reviewed by Miller et al. (248), most attention has been paid to behavioral coping strategies, 12-step approaches, and confrontational interventions (249), all of which are associated with high rates of treatment entry for patients who receive the intervention. However, in helping family members engage their significant others in treatment, concerned significant others and identified patients are more likely to follow through and show better results with less confrontational approaches, including CRA and community reinforcement and family training (250), than with more traditional interventions (248). Couples and family therapy are also useful for promoting psychological differentiation of family members, providing a forum for the exchange of information and ideas about the treatment plan, developing behavioral management contracts and ground rules for continued family support, and reinforcing behaviors that help prevent relapse and enhance the prospects for recovery. There is also some evidence that these approaches can improve the psychosocial functioning and decrease the likelihood of substance use in children living with a parent abusing alcohol or other substances (251, 252).

9. Self-help groups and 12-step-oriented approaches

The most widely available self-help groups (also called *mutual help groups*) are based on the 12-step approach, originally embodied in AA (253, 254), which emphasizes the concept of substance dependence as an incurable, progressive disease that has physical, emotional, and spiritual components. The 12-step programs firmly endorse the need for abstinence and consider themselves lifelong programs of recovery, even though initial success is attained one day at a time. The importance of recognizing and relying on a "higher power" or a power greater than the individual is a central element of these programs. Also key are the 12 steps of recovery, which focus first on surrender and acceptance of one's disease, second on a personal inventory, third on making amends and personal change, and finally on bringing the message to others. In addition, 12-step groups help members with relapse prevention by providing role models, social support, social

strategies for maintaining a sober lifestyle, and opportunities for structured and unstructured substance-free social events and interactions. Members of self-help groups can attend meetings on a self-determined or prescribed schedule, which, if necessary, could be every day or even more than once a day. Periods associated with high risk for relapse (e.g., weekends, holidays, evenings) are particularly appropriate for attendance. A sponsor who is compatible with the patient can provide important guidance and support during the recovery process, particularly when the patient is facing periods of emotional distress and increased craving. The straightforward advice and encouragement about avoiding relapse from a recovering sponsor as well as his or her personalized support are important features of 12-step groups. For clinicians who are treating patients who report involvement in self-help groups, it is useful to ask if they are attending meetings, if they have obtained a sponsor, and if they are attending other activities associated with the self-help group (e.g., self-help group–sponsored social gatherings, retreats).

Another significant advantage to 12-step groups is their broad availability. AA is a worldwide organization with an estimated 2.2 million members in 150 countries (255), and 12-step groups have expanded to include treatment of nearly every type of substance use (Cocaine Anonymous, Marijuana Anonymous, Methadone Anonymous, Narcotics Anonymous, Nicotine Anonymous, "Crystal Meth" Anonymous). Self-help groups based on the 12-step model are also available for family members and friends (e.g., Al-Anon, Alateen, Nar-Anon) and provide group support and education about the disorder, with the goal of reducing maladaptive enabling behavior in family and friends.

In general, active participation in self-help groups has been correlated with better outcomes (256). AA has been effective for both men and women and appears to be particularly useful for those with more severe alcohol dependence (257–259). Other recent research has suggested that 12-step groups may also benefit patients dependent on substances such as cocaine (256). For patients concurrently receiving professional substance abuse treatment, there is growing empirical evidence that improved treatment outcomes are associated with participation in self-help groups (260–266). Furthermore, several studies (43, 219, 265, 267) support the efficacy of professional treatment, including TSF therapy (268) and individual drug counseling (269), that enhances a patient's motivation to participate in 12-step programs. These findings have important clinical implications, given that these approaches are similar to the dominant model applied in most community treatment programs (270). Thus, for many patients, even those who may still be actively using substances, referral to a 12-step program can be helpful at all stages in the treatment process.

An individual's refusal to participate in a self-help group is not synonymous with his or her resistance to treatment in general. Despite their many potential benefits, self-help groups are not useful for all patients. Some individuals' apparent resistance to self-help group participation can be addressed by individualizing the choice of a group to the patient's needs. For example, young people generally do better in groups that include age-appropriate peers in addition to some older recovering members. Patients who require psychotropic medications for co-occurring psychiatric disorders should be directed to groups in which this activity is recognized and supported as useful treatment rather than as another form of substance abuse. The spiritual tenets of traditional 12-step programs can be a deterrent to participation for individuals who do not embrace these ideas. Although not widely available, alternative self-help groups such as Women for Sobriety (271), Secular Organizations for Sobriety (272), and Self-Management and Recovery Training (273) have been developed to address this problem and may be an option for some patients.

10. Brief therapies

The efficacy of brief interventions has been studied mostly in connection with alcohol use disorders. The interventions were initially designed to facilitate the treatment of alcohol abuse or dependence in a setting other than a substance abuse treatment facility (e.g., primary care clinic,

mental health clinic, EAP) (274, 275). More recent evidence suggests that brief interventions are also effective with other substance use disorders, including cannabis (276), opioid (277), and nicotine (278) dependence and in special populations such as adolescents (279), patients with co-occurring psychiatric and substance use disorders (280), and patients in the military (281).

The A-FRAMES model is the core structure of a brief intervention: **A**ssessment, providing objective **F**eedback, emphasizing that **R**esponsibility for change belongs to the patient, giving clear **A**dvice about the benefits of change, providing a **M**enu of options for treatment to facilitate change, using **E**mpathic listening, and emphasizing and encouraging **S**elf-efficacy with the patient (49). Despite the short time required to implement a brief intervention, treatment facilities that do not specialize in substance abuse treatment often experience difficulties in using this strategy, including inadequate time available during face-to-face encounters and clinicians' negative attitudes toward substance use (282, 283).

11. Self-guided therapies

Self-help therapies guided by written, programmed, or Internet-based instruction have been shown to be effective for heavy users of legal substances (i.e., alcohol, nicotine) who do not meet criteria for a substance use disorder. The target population for such approaches typically includes students or general medical patients rather than individuals who are seeking treatment for a substance use disorder.

Self-help manuals and behavioral self-control training teach patients how to 1) set goals for substance reduction or cessation, 2) monitor progress toward achievement of these goals, 3) reward oneself for progress, 4) learn new coping skills that will facilitate substance reduction or abstinence, and 5) perform functional analysis of behaviors associated with substance use (284). These therapies are available as manual-guided self-help programs, manual-guided therapies with a clinician, and computer-guided programs (285, 286). They are therefore available for home use as well as office- and clinic-based use.

Although these approaches are sometimes helpful for those at high risk for developing a substance use disorder or substance-related medical consequences, such minimal therapies may not be sufficient for treatment-seeking patients who already have a substance use disorder.

12. Hypnosis

The use of hypnotherapy for substance use disorders has been most studied as an aid in the cessation of cigarette smoking, with its usual goal being to implant unconscious suggestions that will deter use of a substance, such as "smoking will be unpleasant." Despite the widespread use of hypnosis in this context, there is little scientific validation to support its effectiveness in the treatment of nicotine dependence (287).

▶ G. CLINICAL FEATURES INFLUENCING TREATMENT

1. Use of multiple substances

Many patients entering treatment for a specific substance use disorder abuse more than one substance, and co-occurring nicotine dependence is particularly common. For some patients, there is a "drug of choice," with other substances serving as a substitute when the primary substance is unavailable. Others routinely use multiple substances simultaneously. An individual's concurrent use of two or more substances may be motivated by his or her wish to modify the effects of the primary drug of choice or to prevent or relieve withdrawal symptoms. In addition, many patients use multiple substances because of their availability. Frequent drug combinations include 1) cocaine and alcohol; 2) cocaine and heroin; 3) heroin and benzodiazepines; 4) alcohol, cocaine, and benzodiazepines; 5) nicotine and any other drug; 6) multiple "club

drugs" (e.g., 3,4-methylenedioxymethamphetamine [MDMA], γ-hydroxybutyrate [GHB], ketamine); 7) "club drugs" with prescription medications (e.g., MDMA with sildenafil and/or fluoxetine); and 8) opioids, stimulants, sedatives, steroids, and other substances. The severity of abuse of each substance and the motivation to stop using each substance may vary widely in individuals who abuse multiple substances.

The treatment of patients using multiple substances may be complicated by 1) simultaneous intoxication or withdrawal from two or more drugs, 2) varying time frames for experiencing withdrawal symptoms, 3) the need to detoxify the patient from more than one drug, and 4) potential interactions between an abused substance and medications used to treat a comorbid substance use disorder (e.g., inadvertent precipitation of opioid withdrawal in patients treated with naltrexone for alcohol dependence).

Although the presence of multiple substance use disorders is the norm, there is limited research to guide clinicians on adapting the usual evidence-based clinical interventions to the treatment of individuals using more than one substance, including medication and psychosocial treatments. The best recommendation is for the clinician to do a comprehensive assessment of the patient and integrate the evidence-based treatment approaches, including pharmacological and psychosocial treatments, for each specific substance use disorder (288).

2. Psychiatric factors

The presence of a substance use disorder will have an impact on psychiatric issues, such as the risk of suicide or other self-injurious behaviors and the risk of aggressive behaviors, including homicide. In addition, the presence of co-occurring psychiatric symptoms or disorders affects the patient's treatment adherence as well as the onset, course, and prognosis of the substance use disorder (170, 288–292). These factors need to be taken into consideration when arriving at a treatment plan for an individual patient.

a) Risk of suicide

The frequency of suicide attempts and death by suicide is substantially higher among patients with a substance use disorder than in the general population. A systematic review of retrospective and prospective cohort studies of substance use disorders and suicide (293) demonstrated that individuals with alcohol use disorder, opioid dependence, or mixed drug use have a substantially greater likelihood of suicide compared with the general population, with a 9.8-, 13.5-, and 16.9-fold elevated risk, respectively. This review reported insufficient evidence to compare the suicide risk among patients with other drug use disorders (e.g., cocaine dependence). In terms of lifetime suicide mortality, a review of 83 studies demonstrated a lifetime suicide risk of 7% in individuals with an alcohol use disorder, which is comparable to that of individuals with a mood disorder (6%) or schizophrenia (4%) (294). These rates vary by country and may be slightly lower in the United States (295). In addition, significant rates of substance use disorders are found in psychological autopsy studies of individuals who have died by suicide (296–300), with a recent or impending interpersonal loss being a frequent apparent precipitant (301).

Rates of suicidal ideation and suicidal behaviors, including suicide attempts, are also increased in individuals with a substance use disorder. For example, in a recent prospective study, treatment-seeking individuals with alcohol dependence were found to have attempted suicide seven times more frequently than age-matched, non-alcohol-dependent comparison subjects during the 5-year follow-up period after the initial evaluation (302). The alcohol-dependent individuals who attempted suicide (4.5%) were more likely than the other individuals to have made prior attempts; other related factors were earlier onset of the substance disorder, more severe substance dependence, dependence on multiple substances, more panic symptoms, being separated or divorced, having had prior treatment, and having been diagnosed with a substance-induced psychiatric disorder (302). In addition, significant high rates of substance use disorders are seen among individuals who have attempted suicide (296, 303–305).

The risk of suicidal behaviors and death by suicide is further increased for individuals with a substance use disorder in the context of certain co-occurring psychiatric disorders, such as major depressive disorder, bipolar disorder, and cluster B personality disorders. The presence of major depressive disorder substantially increases impulsive suicidal behaviors and suicide risk (298, 303, 306–308). A recent review of the literature on co-occurring alcohol use disorders and major depressive disorder demonstrated that this comorbidity increases the risk of suicidal ideation, suicidal behaviors, and death by suicide (309). Among patients diagnosed with major depressive disorder and bipolar disorder, cigarette smoking has also been found to be an independent predictor of future suicidal behavior (310).

Prospective studies of patients with co-occurring bipolar and substance use disorders consistently report greater frequency of lifetime suicide attempts and suicidal ideation compared with bipolar disorder patients with no co-occurring substance use disorder (311–313). Bipolar patients with co-occurring anxiety symptoms or cluster B personality disorder features and a substance use disorder may be at the greatest risk for suicidal behaviors (314, 315).

Patients with co-occurring cluster B personality and substance use disorders also have a greater risk of suicidal ideation and death by suicide (316, 317). This population is also at greater risk for accidental death by injection drug overdose (318).

Despite this clear evidence for an increased risk of suicidal behaviors in individuals with a substance use disorder, few controlled studies are available to assist in guiding the treatment of such patients (319). As in the care of any patient with a psychiatric disorder, suicide risk should be assessed regularly and in a systematic manner. Assessment of suicide risk includes determining the presence or absence of current suicidal thoughts, intent, and plan; a history of suicide attempts (e.g., lethality of method, circumstances); a family history of suicide; a history of aggression (e.g., weapon use, circumstances); the intensity of current depressive and other mood symptoms; the current treatment regimen and response; recent life stressors (e.g., marital separation, job loss); substance use patterns; psychotic symptoms; and current living situation (e.g., social supports, availability of weapon). In substance-using individuals, suicidal ideation and suicide attempts may occur in the context of a major depressive episode or result from substance-induced sadness or dysphoria combined with increased impulsivity and poor judgment. However, individuals with a substance use disorder can also be at risk for suicide even in the apparent absence of depression. In terms of treatment implications, care should be used when prescribing potentially toxic medications to a suicidal patient. For additional recommendations on the assessment and treatment of suicidal patients with substance use disorders, the reader is referred to APA's *Practice Guideline for the Assessment and Treatment of Patients With Suicidal Behaviors* (301).

b) Risk of aggressive behaviors, including homicide

Substance use disorders are associated with an increased risk for aggressive behaviors toward others, including physical assault, sexual aggression, domestic violence, child abuse, and homicide (320–322). Substance intoxication and withdrawal states may be associated with anxiety, irritability, agitation, impaired impulse control, disinhibition, decreased pain sensitivity, and impaired reality testing; these effects are hypothesized to account for the increased aggressive behaviors associated with substance use. In particular, intoxication with substances such as alcohol, cocaine, methamphetamine, PCP, anabolic steroids, and hallucinogens may be associated with aggression (138, 323–327), whereas withdrawal from substances such as alcohol, opioids, sedative-hypnotics, and cannabis can lead to withdrawal syndromes associated with a risk of aggressive behaviors (138, 320, 328). Intoxication with marijuana or hallucinogens may inadvertently lead individuals to perform aggressive acts because of a faulty perception of reality coupled with high levels of anxiety and paranoia (329–331). Substance use disorders are also indirectly associated with aggressive behaviors engaged in to obtain illicit or expensive substances. Although it is important to assess for and be aware of the potential for aggressive be-

haviors in individuals with a substance use disorder, it is also important to assess for substance use disorders in all individuals who present with a history of agitation or aggression. Because family and partners may be affected by substance-related domestic violence, systematic screening and referral for domestic violence treatment interventions may effectively reduce domestic violence. Some treatments such as abstinent partner therapy (e.g., coping skills training [332]) and couples therapy (e.g., behavioral couples therapy [333]) have been shown to reduce alcohol-related domestic violence in randomized, controlled trials.

c)   Sleep disturbances

Individuals with substance use disorders frequently report sleep disturbances, particularly after being detoxified. For some patients, managing sleep disturbances will be an important component of the treatment plan. Indeed, some studies have demonstrated that among detoxified alcohol-dependent individuals, insomnia is a strong predictor of relapse (334–336). Despite the recognition that sleep disturbances are a problem among individuals with substance use disorders, only a handful of studies have examined the treatment of sleep disturbances in these individuals, and these studies have focused only on individuals with alcohol dependence. For example, one small double-blind study found that trazodone was superior to placebo in improving sleep in alcohol-dependent individuals with insomnia (337). In an open-label study comparing trazodone and gabapentin for the treatment of insomnia in alcohol-dependent individuals, both medications were found to improve insomnia, but the gabapentin group showed greater improvements than the trazodone group (338). Given the open-label nature of this study, more research is needed to determine if gabapentin is an effective treatment for sleep disturbances related to alcohol dependence. In addition, more research is needed to determine if trazodone and gabapentin, as well as other sedating psychotropic medications, can effectively treat sleep disturbances not only in individuals with alcohol dependence but also in those with other substance use disorders.

In addition to the studies of pharmacological agents, there has been one randomized, controlled study that showed that CBT strategies helped improve sleep disturbances in alcohol-dependent individuals in recovery (339). As with the pharmacological treatments for sleep disturbances, more research is needed to determine if these strategies will help improve insomnia in individuals with other substance use disorders as well.

d)   Co-occurring psychiatric and substance use disorders

(1) General principles

Co-occurring psychiatric and substance use disorders are common in all treatment settings (e.g., centers for the treatment of substance use disorders, mental health clinics, primary care settings, emergency departments) and in the general community. In fact, only a few differences (e.g., higher prevalence of schizophrenia and primary psychotic disorders in mental health care settings, more severe patterns of substance use in substance use treatment settings) are observable between patients with co-occurring psychiatric disorders receiving treatment in substance abuse treatment centers and patients with co-occurring substance use disorders receiving treatment in mental health treatment centers (340). In community population samples studied in the National Comorbidity Survey (341), individuals with alcohol dependence had high rates of clinically significant depression during their lifetime (men: 24% depression and 11% dysthymia; women: 49% depression and 21% dysthymia). Individuals with bipolar disorder had high rates of alcohol (61%) and other substance (41%) dependence (342). Treatment-seeking individuals have even higher rates of co-occurring disorders (343–345). For example, Penick et al. (346) studied a U.S. Department of Veterans Affairs (VA) hospital outpatient population with alcohol dependence or abuse and found that 56% reported co-occurring psychiatric disorders. In substance use disorder treatment settings, depression, anxiety, and personality disorders frequently occur. However, posttraumatic stress disorder (PTSD), adult ADHD, learning

disabilities, social anxiety disorder, eating disorders, and pathological gambling are also common and are often underrecognized and undertreated (121, 288).

Individuals with nicotine dependence are more likely to have co-occurring psychiatric disorders than the general U.S. population (347). Furthermore, in mental health and substance use disorder treatment settings, nicotine dependence continues to be the most common co-occurring substance use disorder, with approximately 60%–95% of patients being nicotine dependent, although this varies by the type of psychiatric disorder and the treatment setting (348). One analysis of nicotine use as reported in the National Comorbidity Survey found that individuals with psychiatric disorders were about twice as likely to smoke as the general population and that about 44% of the cigarettes smoked in the United States were smoked by individuals with a psychiatric disorder (349).

Use of multiple substances and co-occurring psychiatric and substance use disorders are now so common in treatment settings that these combinations should be expected. Thus, all patients with a substance use disorder should be carefully assessed for the presence of co-occurring psychiatric disorders, including additional substance use disorders. Conversely, patients with identified psychiatric disorders should be routinely assessed for the presence of a co-occurring substance use disorder (350, 351).

Treating individuals with co-occurring psychiatric and substance use disorders in traditional inpatient and outpatient programs is challenging. Patients' motivation to change may vary according to the type of substance(s) they use and the severity of their psychiatric issues, and this needs to be taken into consideration in treatment planning. Recent research and consensus opinions by experts in the field support the notion that the integration of substance abuse and mental health treatment strategies, including integrated systems, programs, and clinical treatment, improves patient outcome (80, 121, 352, 353). There is growing evidence that patients in psychiatric or substance abuse treatment settings have better outcomes if they receive integrated treatment for their coexisting psychiatric and substance use disorders (121, 288, 354–356). Integrated treatment usually requires incorporating and modifying traditional psychiatric and substance abuse treatment methods so that the co-occurring disorders receive simultaneous treatment.

a. Integrated treatment

Recent research and clinical experience (80, 288) has also shed light on the question of treatment timing (e.g., if co-occurring disorders should be treated together in an integrated manner or in what circumstances one problem should be addressed before another). In general, the length of the observation period for a psychiatric or substance use disorder will be determined by balancing the following considerations: the degree of diagnostic certainty, the severity of the patient's condition, and the anticipated benefits and risks of the proposed treatment (288, 353).

The integrated treatment of co-occurring psychiatric and substance use disorders can include psychosocial and/or pharmacological interventions. Initial treatment efforts should include engaging the patient in treatment and assessing and managing the most severe symptoms of both types of disorders. This may include addressing symptoms of intoxication or withdrawal. Sometimes severe psychiatric symptoms (e.g., psychosis, suicidal ideation) can be managed while a patient is intoxicated or experiencing withdrawal; such patients may require immediate treatment in an emergency department or an inpatient psychiatric unit. Once a patient's acute psychiatric symptoms and intoxication or withdrawal states have been stabilized, the patient can be evaluated for treatment in an ongoing rehabilitative treatment program. When patients are being treated in a substance abuse treatment setting, their psychiatric symptoms should be monitored and addressed clinically through psychiatric medications, when appropriate, as well as through integrated psychosocial strategies (e.g., teaching patients mood management as part of relapse prevention therapy) and integrated treatment approaches for psychiatric disorders and substance use disorders (357).

In a psychiatric treatment setting, it would be incorrect to assume that successful treatment of a psychiatric disorder will resolve the substance use disorder. The substance use disorder will require specific treatment even when it arises in the context of another psychiatric disorder, a situation that is quite common and that presents an opportunity for the prevention of a secondary disorder (358).

Certain psychosocial and pharmacological treatments have been studied for specific combinations of psychiatric and substance use disorders (e.g., major depression and alcohol dependence, schizophrenia and cocaine dependence) (288, 353); the literature about these treatments is presented in the specific substance use disorder sections of this practice guideline. The reader is also advised to review other APA practice guidelines for the treatment of patients with specific psychiatric disorders for additional information.

b. Pharmacological management of psychiatric disorders

In most patients, the same medications are recommended for the treatment of a specific psychiatric disorder whether that disorder co-occurs with a substance use disorder or not. Clinical issues such as medication tolerability, safety, and abuse potential are important considerations in choosing a medication and will influence traditional psychopharmacological treatment algorithms. There is no evidence to suggest that the duration of pharmacotherapy for a psychiatric disorder in conjunction with a co-occurring substance use disorder would differ from that needed to treat the psychiatric condition alone, and there are no data to suggest that decisions about continuation and maintenance treatment should differ (288). An important clinical question in treating a co-occurring psychiatric disorder in a substance use disorder treatment setting is whether the prescribing clinician should initiate psychiatric medications during the acute treatment of the substance use disorder. For some psychiatric disorders (especially depression, generalized anxiety disorder [GAD], social anxiety disorder, and PTSD), there have been widely differing opinions about the amount of time a patient should be abstinent from a substance before a definitive diagnosis of a co-occurring psychiatric disorder versus a substance-induced psychiatric disorder can be made. If there is little overlap between the symptoms observed and the expected abstinence syndrome (such as bulimia nervosa in an opioid-dependent patient), then the psychiatric diagnosis can be immediately established. In circumstances when prominent mood or anxiety symptoms could be equally attributable to early abstinence or an independent co-occurring psychiatric disorder, a clinician may consider whether similar symptoms occurred before the substance use or during previous abstinence periods or whether the individual's family history suggests a vulnerability to a co-occurring mood or anxiety disorder. A common recommendation is to consider the severity of an individual's functional impairment when deciding whether or not to initiate pharmacotherapy, continue ongoing monitoring of symptoms, and initiate psychosocial treatment strategies for the management of anxiety and depression (288).

Medication nonadherence is common among individuals with co-occurring psychiatric and substance use disorders (359, 360). Nonadherence can be due to many factors, including cognitive impairment, the patient's fear of the interaction between prescribed medication and substances being abused, fear that the prescribed medication is itself harmful, change in motivation, and lack of support. Some patients attending 12-step meetings may feel pressure from some group members not to take psychiatric medications because they are "mood altering"; however, AA does support the appropriate use of needed medications (361, 362). AA brochures and other resources do state a reasonable concern about individuals' avoiding psychotropic medications with an abuse potential (e.g., sedative-hypnotics, anxiolytics, stimulants). When such medications are necessary, a clinician should prescribe them with caution and closely monitor their use (e.g., dispense in limited quantities, track prescription refills, monitor ongoing medical necessity for and the patient's response to the medication).

c. Medications to treat substance use disorders

Medications for treating substance use disorders, such as those for managing acute withdrawal and protracted withdrawal symptoms or reducing craving, have not been well studied in dually diagnosed populations but should be considered for these patients. The presence of a co-occurring mental illness may influence a clinician's decision to prescribe disulfiram for alcohol-dependent patients if, for example, the clinician is concerned about a patient's capacity to adhere to prescribing instructions due to acute psychiatric symptoms. However, a 12-week multicenter, randomized, controlled trial of disulfiram in patients with co-occurring alcohol dependence and psychiatric illness demonstrated the safety and effectiveness of this medication with this population (363). This same study also substantiated the safety and efficacy of naltrexone use in this population. However, no further benefit was achieved in this study by combining disulfiram and naltrexone.

d. Integrated psychosocial treatments

Psychosocial treatment is very important in the treatment of a substance use disorder both with and without a co-occurring psychiatric disorder. Integrated psychotherapy approaches represent some of the most recent advances in psychosocial treatments, and several have been developed for specific subtypes of co-occurring disorders. A common feature of these integrated therapies is their blending of traditional evidence-based psychotherapies with traditional evidence-based substance use disorder therapies such as MET, relapse prevention therapy/CBT, and TSF therapy. Examples of psychiatric disorders for which integrated treatments have been developed include PTSD (364–368), bipolar disorder (369), schizophrenia (80, 360, 370–372), and personality disorders (373, 374). The efficacy of these integrated psychotherapies is being actively investigated in individual as well as in family and group modalities (375–377).

(2) Treatment in the presence of specific co-occurring psychiatric disorders

a. Schizophrenia

A review of the literature examining nicotine dependence among individuals with schizophrenia demonstrated prevalence rates of 68%–88% among outpatients and 81%–88% among inpatients (378), suggesting that substance use vulnerability alone cannot account for the high smoking rates among patients with schizophrenia. Patterns of nicotine use among patients with schizophrenia are more severe than in patients with other psychiatric diagnoses (379), and these usage patterns are associated with increased morbidity and mortality due to tobacco-related medical diseases such as cancer and cardiovascular and respiratory diseases (359, 380–383). Apart from nicotine dependence, about 40%–60% of individuals with schizophrenia will have another co-occurring substance use disorder during their lifetime (353, 384, 385). Substance-abusing individuals with schizophrenia are more likely to be male, young, and less educated and have better social skills than those not abusing substances, but they have less peer support and poorer treatment outcomes in traditional substance abuse treatment settings because of the stress associated with the confrontational treatment approaches sometimes used in these programs (353, 386). Because substance abuse treatment staff typically have limited training in managing psychosis and because mental health clinicians are trained and able to provide both medications and psychosocial treatment for schizophrenia, this population most commonly receives integrated treatment for the co-occurring disorders within the mental health system.

Effective integrated treatment programs have used one clinical team to provide long-term, comprehensive care (i.e., medication and psychosocial treatment interventions) for both psychotic and substance use disorders (80, 353). Treatment is provided in the patient's natural environment, is matched to the patient's motivational state, provides comprehensive community services (e.g., stable housing, financial assistance through entitlements, vocational rehabilitation), and is not limited in duration (80, 387). Integrated treatment often begins by stabilizing a patient's psychotic symptoms, which may require psychiatric hospitalization. Integrated treat-

ment programs can then initiate substance abuse treatment when the patient is sufficiently stable to participate in the psychosocial treatments for the psychiatric and substance use disorders. Thus, the acute stabilization phase may initially emphasize appropriate antipsychotic and psychosocial treatments that help stabilize the illnesses (353, 371).

   1)   *Pharmacotherapy*

Existing studies and reports from expert consensus meetings on co-occurring disorders support the same first-line agents recommended in APA's *Practice Guideline for the Treatment of Patients With Schizophrenia* (388) for individuals with co-occurring schizophrenia and substance use disorders (80, 288). With the possible exception of clozapine for patients with treatment-resistant symptoms, antipsychotics generally have similar efficacy in treating the positive symptoms of schizophrenia (389), although there is emerging evidence and an ongoing debate regarding whether second-generation antipsychotics may have superior efficacy in treating global psychopathology and cognitive, negative, and mood symptoms (388). Various smaller studies have found better outcomes with clozapine (390–398), risperidone (394, 399–402), and olanzapine (403, 404) than with first-generation antipsychotics for patients with co-occurring schizophrenia and substance use disorders. However, most of these studies were retrospective, nonrandomized, or uncontrolled pilot studies. Furthermore, no evidence to date suggests that any one second-generation antipsychotic is more efficacious than another in this population, and no trials have been reported that compare these agents in the same clinical study. Some have thought that clozapine should be considered as a first-line agent in patients with schizophrenia co-occurring with a substance use disorder because of the number of studies supporting its use (394) and its ability to reduce the risk of suicidal behaviors (405). In addition, clozapine may have beneficial effects in decreasing smoking (406–408). However, most experts have continued to recommend clozapine as a second-line agent (288) because of the need for regular monitoring of the patient's white blood count to detect granulocytopenia or impending agranulocytosis, as well as other concerns about clozapine's side-effect profile (i.e., increased seizure risk and sedation). Because significant nonadherence to clozapine necessitates the retitration of the medication dose and because blood monitoring is an essential part of clozapine treatment, clozapine is generally used in more motivated patients and in well-integrated treatment programs.

In choosing an antipsychotic medication, a clinician should assess patient preferences and vulnerabilities regarding side effects, interactions with abused substances, and other safety considerations. It should be noted that individuals with schizophrenia who abuse alcohol and cocaine may have an increased risk for seizures or liver toxicity and may have cardiac abnormalities as a result of their substance use. Medications that may induce QT prolongation should be used with caution, with electrocardiographic monitoring as needed. Because most antipsychotic medications are hepatically metabolized and can lower seizure threshold to some degree, these factors should also be taken into consideration when choosing among antipsychotic medications. Patients with schizophrenia may also experience increased somnolence and orthostatic hypotension if they abuse alcohol or other sedating drugs while taking antipsychotic medications. Tobacco smoking substantially lowers blood levels of clozapine, olanzapine, and numerous first-generation antipsychotics (e.g., haloperidol, fluphenazine, chlorpromazine, thioridazine) by increasing cytochrome P450 (CYP) 1A2 enzyme hepatic metabolism, a moderate effect that may necessitate an increase in the medication dose. The metabolism of other second-generation antipsychotics is not significantly affected by changes in smoking status.

Another clinically important issue in this population is addressing poor adherence with both pharmacological and psychosocial interventions. The use of long-acting, injectable antipsychotic medications can help increase medication adherence. A long-acting, injectable form of the second-generation antipsychotic risperidone is available as are long-acting decanoate preparations of first-generation antipsychotics (i.e., haloperidol, fluphenazine); there have been no direct comparisons of these long-acting first- and second-generation antipsychotic agents in this population.

In general, medications targeting specific substance use disorders can be safely prescribed for patients with co-occurring schizophrenia and substance use disorders (288). However, careful assessment is indicated before initiating treatment with disulfiram. Given the cognitive difficulties associated with schizophrenia, disulfiram should be reserved for use in individuals whose judgment and memory are adequate and for whom impulsivity is not a significant concern. In addition, there may be some further concern about using high-dose disulfiram in this population because carbon disulfide, a metabolite of disulfiram, inhibits dopamine β-hydroxylase, increases dopamine levels, and could potentially worsen psychosis (409, 410). Specific studies also support the use of naltrexone for alcohol dependence and methadone for opioid dependence in this population (411–413). The treatment of nicotine dependence with NRTs (i.e., nicotine patch, gum, spray, inhaler, or lozenge) and bupropion has helped improve treatment outcomes for tobacco smokers with schizophrenia (414, 415). There is a theoretical concern that bupropion may increase psychotic symptoms; however, this concern has not been borne out in studies to date (414). There are improved outcomes with combining NRT and bupropion with psychosocial treatments that are specific to nicotine dependence (348, 416).

2) Psychosocial treatments

Integrated psychosocial treatments for individuals with co-occurring schizophrenia and substance use disorders most commonly occur in mental health settings and include unique psychotherapy approaches as well as modified treatment programs and systems (352). One key aspect of integrated treatment is that patients do better when clinicians are able to maintain an optimistic, empathic, and helpful approach (417). Integrated programs often provide comprehensive services, including active outreach and case management in the community setting, in an effort to better engage and retain patients and help them transition between different levels of care (370, 417). Model integrated treatment programs have been described and evaluated in the literature (417), including assertive community treatment teams and integrated stage-based motivational models; these models tend to emphasize a recovery-oriented perspective while combining medications, MET, relapse prevention therapy, social skills training, and specific dual recovery therapy approaches (80, 371, 386, 418, 419). Other helpful components to integrated treatment programs include contingency management and money management (360, 372). Money management helps patients prevent relapse, given that many receive Social Security disability or Supplemental Security Income payments and are most vulnerable to substance use and relapse soon after receiving these funds (372).

b. Depressive disorders

Major depressive and substance use disorders commonly co-occur in clinical populations and in the community (341, 343, 344, 420). Studies have demonstrated that individuals diagnosed with major depressive disorder have high lifetime co-occurrence rates of alcohol abuse (men 9% and women 30%) and alcohol dependence (men 24% and women 48.5%) (421). Among individuals with major depressive disorder, approximately 25% have a co-occurring substance use disorder (422). A large prospective, longitudinal study has demonstrated that alcohol and drug use disorders during adolescence predict later development of major depressive disorder in young adults (423).

Mood disturbance is one of the most common symptoms reported by individuals in substance use disorder treatment programs. In addition to the high rate of co-occurring major depressive and substance use disorders, patients in substance use disorder treatment settings frequently experience substance-induced mood disorders in which signs and symptoms of depression are related to acute substance intoxication or to acute or protracted withdrawal from substances; these symptoms remit with maintained abstinence (424). Because it is often difficult for a clinician to discern whether a cluster of symptoms is due to co-occurring major depressive disorder, substance intoxication, substance withdrawal, substance-induced mood

disorder, or some combination thereof, guidelines have been established for diagnosing and treating mood symptoms in the context of a substance use disorder (425). When possible, it is advisable to delay antidepressant pharmacotherapy by 1–4 weeks, depending on the nature and severity of the mood symptoms, to allow the clinician to identify substance-induced mood symptoms that may remit without medication intervention.

In general, treatment of depressive symptoms of moderate to severe intensity should begin concurrently or soon after initiating treatment of the co-occurring substance use disorder, particularly if there is evidence of prior mood episodes. In individuals without prior episodes of depression or a family history of mood disorders, it may be appropriate to delay the treatment of mild to moderate depressive symptoms for the purpose of diagnostic clarification. Clinicians are advised to monitor symptoms, assess and reassess for suicidal ideation, provide education, encourage abstinence from substances, and observe changes in mental status during the substance-free period while actively considering whether antidepressant intervention is indicated (288, 426–429).

1) Pharmacotherapy

Existing studies and expert consensus support the use of first-line agents recommended in APA's *Practice Guideline for the Treatment of Patients With Major Depressive Disorder* (430) and substance use disorder medications for detoxification, protracted withdrawal, and agonist maintenance treatment (288). Randomized, controlled trials supporting the efficacy of antidepressant pharmacotherapies for co-occurring major depressive disorder and specific substance use disorders exist for alcohol dependence, opioid dependence, cocaine use disorders, and nicotine dependence.

A meta-analysis of 14 well-designed placebo-controlled trials of antidepressant medication for co-occurring major depression and alcohol, opioid, or cocaine dependence (425) showed an overall beneficial effect of medication on mood outcome, similar in magnitude to the effect size observed in clinical trials involving depressed patients without substance problems. Studies showing the largest effects of medication on mood outcome also showed significant beneficial effects of medication on self-report measures of substance use, although rates of abstinence were low. The results across studies were inconsistent, with eight positive and six negative studies. The positive studies, those demonstrating a beneficial effect of antidepressant medication, had low placebo response rates and were more likely to have required at least a week of abstinence prior to diagnosing depression and starting medication. The evidence for medication effectiveness was more consistent among studies of patients with alcohol dependence than among studies of patients with drug dependence, in agreement with the conclusion of another recent meta-analysis (430a).

Of the selective serotonin reuptake inhibitors (SSRIs), fluoxetine (431) and sertraline (432–434) have been studied in the treatment of co-occurring major depressive disorder and alcohol dependence, and evidence is also available for the use of nefazodone (435, 436) and the tricyclic antidepressants (TCAs) imipramine (428, 437) and desipramine (438). These agents, however, have not been compared with each other nor has there been an adequate number of studies of other SSRIs to make recommendations for specific antidepressants as first-line agents in this population. A review of the literature indicates that antidepressant treatment is more effective in ameliorating mood symptoms than in improving drinking outcomes for this dually diagnosed population (439). Given the reported risks of hepatotoxicity and death with nefazodone use (440), this medication is not generally recommended unless other therapies have failed.

The evidence base for antidepressant pharmacotherapy in co-occurring opioid dependence and major depressive disorder is inconsistent and well studied only in methadone-maintained populations. Results of randomized, placebo-controlled trials of TCA treatment are mixed, with some showing no differences between antidepressant treatment and placebo (441–443) and others showing superior efficacy of TCAs compared with placebo (444–447). Evidence for SSRI

efficacy in the same population is weaker (448), and many studies have failed to demonstrate beneficial effects of SSRIs on mood symptoms (413, 449, 450). Nevertheless, the relative safety of SSRIs as compared with TCAs in this population continues to influence the choice of SSRIs as first-line agents for patients with co-occurring opioid use disorder and major depressive disorder. Although the duration of antidepressant treatment in these studies was not >3 months, there are no available data to suggest that the duration of an antidepressant trial should be different than that used for treating major depressive disorder without a substance use disorder.

Treating mood symptoms in individuals with co-occurring cocaine use and major depressive disorders is complicated by the frequent occurrence of depressive symptoms during acute withdrawal from cocaine. Some randomized, controlled trials support the use of antidepressant intervention in these individuals (451, 452); this population also appears to have a more favorable mood response to TCAs than to SSRIs (453).

Nicotine dependence commonly co-occurs with major depressive disorder. In large well-designed, placebo-controlled trials, the antidepressant medications bupropion (158, 454) and nortriptyline (455, 456) have been found to improve smoking cessation rates and to prevent relapse after successful quit attempts. Smokers with a current major depression were excluded from these studies. The beneficial effects of both nortriptyline (456) and bupropion (454, 1587) have been shown not to depend on a past history of major depression—that is, the medications are equally effective for smokers with and without past depression. An analysis of mediators of treatment effect (456) suggested nortriptyline improves smoking cessation by reducing postquit dysphoria, with the effect, again, independent of past history of major depression. Serious depression sometimes emerges after a patient has successfully quit smoking (457, 457a, 763), suggesting the importance of monitoring mood during quit attempts. Studies are needed of the treatment of smokers with current depressive disorders. However, in such patients, most clinicians will prioritize stabilization of the depressive episode and then subsequently address treatment of nicotine dependence during the maintenance phase of depression treatment (348). Sustained-release bupropion for treating nicotine dependence may be safely added to other antidepressants (e.g., SSRIs, which do not alter smoking cessation rates) being used to treat major depressive disorder (458). NRTs are also recommended as a first-line option in treating nicotine dependence in depressed smokers. In addition, integrating standard tobacco dependence–related psychosocial treatment into ongoing psychosocial treatment for depression improves both tobacco dependence and depression outcomes among smokers with recurrent depression and heavy smoking (459).

Many patients with co-occurring major depressive and substance use disorders will report experiencing insomnia or anxiety symptoms. Such symptoms are optimally addressed using behavioral strategies (e.g., stress reduction, relaxation skills, adherence to sleep hygiene) and/or pharmacological interventions with medications that do not have a potential for abuse (e.g., buspirone) before medications with abuse potential (e.g., benzodiazepines, nonbenzodiazepine hypnotics such as zolpidem) are considered. Although not specifically studied in co-occurring major depressive and substance use disorders, the antidepressant trazodone may represent an additional option (see Section II.G.2.c).

In the context of continued substance use, inadequate symptom improvement should not lead the clinician to conclude that a medication regimen is a therapeutic failure. Patients with persistent depression and substance use may benefit from more frequent outpatient visits or referral to a higher level of care (e.g., intensive outpatient, partial or residential hospitalization, inpatient treatment).

2) Psychosocial treatments

Integrated psychosocial therapies have been developed, and their efficacy is being tested in controlled trials for patients with co-occurring major depressive disorder and substance use disorders (456, 460, 461). These psychotherapy approaches combine traditional therapies for

substance use disorders (e.g., MET, TSF, relapse prevention therapies, CBT, contingency management) with traditional therapies for depression (e.g., cognitive therapy, behavioral therapy, IPT, and brief psychodynamic therapy) (357, 462). These approaches commonly try to help patients identify and manage triggers for substance use, understand and manage feelings, deal with grief and anger, change thoughts and beliefs that worsen mood, improve relationships, and change behaviors and lifestyles (463).

c. Bipolar disorder

Individuals with bipolar disorder are at high risk for a co-occurring substance use disorder; community lifetime prevalence rates of co-occurrence are ≥50% (341, 420). Substance use disorders influence bipolar disorder by worsening each episode as well as worsening the overall course of the disorder by causing more mixed episodes, earlier onset, more frequent episodes, and slower symptom remission (464).

Few medication studies have been conducted with co-occurring bipolar and specific substance use disorders; however, the existing research (464–468) and expert consensus (469, 470) support use of the first-line agents recommended in APA's *Practice Guideline for the Treatment of Patients With Bipolar Disorder* (471) and the use of adjunctive medications that target specific substance use disorders. The few medication studies examining co-occurring bipolar and substance use disorders support the use of valproate (or valproic acid or divalproex) as a mood stabilizer because it shows some evidence of efficacy and appears to help overall treatment adherence (472). In addition, some evidence suggests that patients with these co-occurring disorders are more likely to respond to valproate or a combination of valproate plus lithium than to lithium alone (465–468, 472, 473). The relative lack of efficacy with lithium may be due to an increase in side effects or the difficulty that patients with co-occurring bipolar and substance use disorders have in achieving stable lithium blood levels. The use of carbamazepine in this population is supported by a few studies with positive outcomes (474). There is only one small pilot study to date evaluating the role of second-generation antipsychotics in patients with co-occurring substance use and bipolar disorders (475). Therefore, treatment recommendations follow those presented in APA's *Practice Guideline for the Treatment of Patients With Bipolar Disorder* (471), with first-line pharmacological treatment for more severe manic or mixed episodes with lithium or valproate plus an antipsychotic. For less ill patients, monotherapy with lithium, valproate, or an antipsychotic may be sufficient. Second-generation antipsychotics are generally preferred over first-generation antipsychotics because they appear less likely to cause tardive dyskinesia and extrapyramidal side effects; however, the possibility of weight gain, diabetes, and hyperlipidemia with these agents requires consideration. Second-generation antipsychotic agents with an FDA indication for use in treating acute manic or mixed episodes in bipolar disorder include olanzapine, risperidone, ziprasidone, and aripiprazole. Quetiapine has an FDA indication for the treatment of acute episodes of mania. In the acute setting of a manic episode, a benzodiazepine may be helpful. However, the general concern about using a medication with high abuse potential must be considered; therefore, caution should be exercised in using benzodiazepines beyond the time period of the acute manic episode. For mixed episodes, valproate may be somewhat more efficacious and thus may be preferred over lithium (465–468). Pharmacological alternatives to lithium and valproate include carbamazepine or oxcarbazepine. The possibility of pregnancy should be considered when prescribing valproate or carbamazepine for women of childbearing age, particularly given the increased risk of neural tube defects if the fetus is exposed to these medications in utero.

Because there are no specific studies of the treatment of bipolar depression in substance-abusing individuals, medication strategies should follow the recommendations for managing bipolar depression described in APA's *Practice Guideline for the Treatment of Patients With Bipolar Disorder* (471). The guideline recommends the initiation of lithium or lamotrigine as a first-line pharmacological treatment. Lamotrigine should be used cautiously in individuals with

co-occurring bipolar and substance use disorders because active substance users may be unreliable in reporting rashes; gradual titration of lamotrigine is needed and may be problematic in individuals who may be inclined to take excess medication doses, and drug-drug interactions may alter lamotrigine levels and increase the risk of rash (476). Antidepressant monotherapy is not recommended due to concerns about precipitating a mixed or manic episode or contributing to the development of rapid cycling. As an alternative, especially for more severely impaired patients, some clinicians will initiate simultaneous treatment with lithium and an antidepressant. Also, IPT and CBT may help treat symptoms of bipolar depression when they are added to pharmacotherapy.

Integrated psychosocial treatments for bipolar and substance use disorders have been developed and demonstrated to be effective by Weiss et al. (369). The group therapy–based treatment approach in this study integrated cognitive-behavioral approaches that were effective in treating both disorders. The approach has been described in a clinical treatment manual for clinicians that includes educational, motivational, and coping strategies to enhance medication adherence and self-efficacy with cues and triggers for drug use (369).

Although nicotine dependence is common among individuals with bipolar disorder, there have been no reports on treating nicotine dependence in this population (348). Recommendations for treating co-occurring bipolar disorder and nicotine dependence are to integrate the standard somatic and psychosocial treatments for nicotine dependence (see Section III) into the context of the maintenance phase of treating bipolar disorder.

d. Anxiety disorders

Symptoms of anxiety and anxiety disorders commonly co-occur with substance use disorders (341). Based on a sample of individuals between ages 15 and 54 years, lifetime rates of anxiety disorders (including GAD, panic disorder, specific phobia, social phobia, obsessive-compulsive disorder, PTSD, and acute stress disorder) in the community are estimated to be about 19% in men and 31% in women (341). About 50% of individuals with a substance use disorder have an anxiety disorder (341, 420), with different rates for different anxiety disorders. For example, about 4.5% of patients with a substance use disorder have panic disorder, and 16% of panic disorder patients have a co-occurring substance use disorder (341). Despite the high prevalence rates, anxiety disorders are frequently underdiagnosed in substance abuse treatment settings (477). Because many substances cause state-dependent anxiety symptoms (i.e., during intoxication, acute withdrawal, or protracted withdrawal), the assessment of anxiety disorders in substance-using populations is challenging and requires careful assessment. The clinician should ask about symptoms that relate to specific anxiety disorders and use similar considerations during the assessment process to those recommended for depression symptoms and substance use disorders. Although nicotine dependence is also common among individuals with anxiety disorders, there are almost no treatment studies for this population, and treatment should follow the standard somatic and psychosocial treatment recommendations for nicotine dependence (see Section III).

Integrated treatment for co-occurring anxiety and substance use disorders may include medications and psychosocial treatments from both substance abuse and psychiatric treatment perspectives. Specific medications and CBTs for specific anxiety disorders have been developed and can be combined with the usual treatments for substance use disorders. Providing education about the anxiety and substance use disorders and the effects the disorders have on each other is also important.

The recommended medications for treating panic disorder with a co-occurring substance use disorder are SSRIs plus integrated psychosocial treatment (288, 478). If several SSRIs are tried and found to be ineffective, then a TCA may be considered; however, TCAs may be of concern when using them in the context of co-occurring substance use disorders because of the risk of cardiac toxicity and seizures and the potential for overdose in a suicide attempt. Although benzodiazepines are usually considered a first-line treatment for panic disorder in pa-

tients without an active substance use disorder, the risk of benzodiazepine abuse is a significant concern and precludes this class of medications from being first-line agents in treating panic disorder in the context of a coexisting substance use disorder. In rare cases, physicians have treated severe panic symptoms by using benzodiazepines on a time-limited basis, selecting patients without a history of misusing benzodiazepines but who have a family history of panic disorder, and fully informing the patient and sometimes the family of the risks of taking benzodiazepines. Physicians may also limit prescriptions, supervise medication administration, monitor medication adherence with pill counts, and request that patients come for more frequent office visits while patients are taking benzodiazepines. Two double-blind, placebo-controlled studies have demonstrated the efficacy of buspirone in patients with alcohol dependence and anxiety (479, 480).

Pharmacotherapy for social anxiety disorder in the context of co-occurring substance use disorder may include beta-blockers or SSRIs along with integrated psychosocial treatment. In a recent study in which simultaneous treatment of social anxiety disorder and co-occurring alcohol dependence was compared with treatment of alcohol dependence alone, both treatment conditions improved alcohol-related outcomes and social anxiety; however, treatment focused on alcohol only was associated with better alcohol use outcomes (481). Although more studies of concurrent treatments for social anxiety and substance use disorders are needed, these findings suggest that combination treatment of social anxiety and alcohol use disorders may not be effective for all patients.

The treatment of obsessive-compulsive disorder in the context of a co-occurring substance use disorder uses pharmacotherapy with SSRIs and integrated psychosocial treatment. TCAs, including clomipramine, may be of concern for use in patients with co-occurring substance use disorders because of the risk of seizures and the potential for overdose in a suicide attempt. Second-generation antipsychotics may be an option for some individuals (288).

GAD commonly co-occurs with other psychiatric and substance use disorders. CBT approaches can be particularly helpful for symptoms of preoccupation/rumination and exaggerated perceptions of danger. First-line agents for this population include buspirone and SSRIs. Although benzodiazepines may be used chronically in GAD patients with no substance use disorder, their use should be limited or applied in only the previously described circumstances in patients with a substance use disorder because of their abuse potential (288).

PTSD is common among individuals with a substance use disorder (about 20%), with women having about twice the rate of co-occurring PTSD as men (482); however, clinicians are advised not to overlook the possibility of PTSD in male patients, because in the general community, rates of PTSD are higher for men than for women (483). Rates of PTSD appear to be high in substance use disorder treatment settings, with one study reporting that 40% of 95 substance-abusing/dependent inpatients met criteria for current PTSD (484). Women with PTSD and a substance use disorder often experienced childhood physical and/or sexual abuse, whereas men typically experienced combat or were victims of crime (483). PTSD symptoms are a common trigger of substance use, and patients may perceive the substances as a way of coping with overwhelming emotional pain (485–488). Indeed, one study showed that individuals with PTSD and either cocaine or alcohol dependence experienced increased craving when exposed to both trauma and drug cues (489). As patients with co-occurring PTSD and a substance use disorder participate in treatment and become able to maintain continued abstinence, they may feel overwhelmed by a flood of memories and unprocessed feelings about the past traumas that have been masked by substance use (490). Simply because patients have become abstinent from substances does not mean that symptoms of PTSD have resolved, and these will need to be addressed in treatment (491, 492). Patients may carry a great burden of shame and guilt, as both PTSD and substance abuse may be associated with keeping secrets and denial. These individuals are sometimes perceived as "crazy," "lazy," or "bad" by others and by themselves, and these issues are similarly important to anticipate in psychotherapy (490).

Specific integrated psychotherapies for PTSD co-occurring with a substance use disorder have been developed and evaluated (365, 368, 490). These approaches have similar components in that they educate the patient about both disorders and how the two problems interact to worsen the course of either disorder alone. Treatment focuses on stabilizing the substance use disorder and developing coping skills to manage the PTSD symptoms and trauma memories as they occur during the early phase of abstinence as well as after prolonged periods of abstinence (490). Seeking Safety (490), an empirically tested group treatment for patients with PTSD and a coexisting substance use disorder, and integrated treatment approaches that combine the 12-step treatment model from substance use disorder treatment with traditional psychotherapeutic approaches to PTSD have been developed to treat this patient population (493, 494). One study of 107 women were randomly assigned to receive Seeking Safety treatment, a manual-guided relapse prevention therapy, or standard community treatment found that women receiving Seeking Safety or relapse prevention therapy had significant reductions in substance use, PTSD, and psychiatric symptoms over the 3-month treatment period, whereas the symptoms of women who received standard community treatment worsened (364); furthermore, the Seeking Safety and relapse prevention groups maintained the greater improvements in substance use and PTSD symptoms at the 6- and 9-month follow-ups. Outcomes did not differ between the Seeking Safety and relapse prevention groups.

Many integrated treatment approaches discourage having the patient describe or explore traumatic memories as might be done in exposure therapy. Only a few pilot studies have been published that evaluate trauma exploration therapies (e.g., exposure therapy) in substance-abusing patients (365, 368). In those few studies, positive results were generally reported. One recently published effectiveness trial of integrated exposure-based therapy for PTSD and psychosocial treatment of substance use disorders reported feasibility and clinical effectiveness within an inner-city mental health treatment setting serving dually diagnosed patients (366). Future research is needed to define which patients may benefit from this type of treatment. Other psychosocial treatments used to treat PTSD are being considered for adaptation to patients with PTSD and a co-occurring substance use disorder; these include mourning therapy (495), eye movement desensitization and reprocessing (496), and the counting method (497).

Medication recommendations for treating PTSD in the context of a co-occurring substance use disorder follow the general recommendations from APA's *Practice Guideline for the Treatment of Patients With Acute Stress Disorder and Posttraumatic Stress Disorder* (498). The SSRIs are considered first-line medication treatment for PTSD. Given the abuse potential of benzodiazepines, prescribing them to patients for the treatment of PTSD presents a risk for substance relapse and/or the development of a new substance use disorder.

e. *Attention deficit hyperactivity disorder*

Substance use disorders are common in adolescents and adults with ADHD, with about 33% of adult ADHD patients having a history of an alcohol use disorder and about 20% having a drug use disorder; even higher prevalence rates (50%–60%) of co-occurring nicotine dependence have been reported (341, 499). Among patients with alcohol, cocaine, or opioid dependence, 17%–50% have co-occurring ADHD (499). Establishing a diagnosis of ADHD can be complicated in the context of ongoing substance use, because attention problems are often caused by the acute and prolonged effects of specific substances of abuse, and these attention problems will often improve with prolonged abstinence. On the other hand, delaying adequate treatment of co-occurring ADHD may compromise a patient's capacity to fully participate in treatment for a substance use disorder (500, 501). Therefore, it is recommended that treating physicians attempt to gather evidence supporting a co-occurring ADHD diagnosis (e.g., childhood ADHD, evidence of symptoms during prolonged abstinence from substance use) during early assessment and treatment planning. Clinicians are also advised to assess patients with co-occurring ADHD and a substance use disorder for other commonly co-occurring psychiatric

disorders (e.g., learning disorders, mood and anxiety disorders, conduct disorder/antisocial personality disorder) (499).

The occurrence of childhood ADHD contributes independently of other psychiatric disorders to the risk of developing an early-onset substance use disorder (502, 503). Early interventions for childhood ADHD (psychosocial and/or pharmacotherapy) may help to prevent new-onset substance use disorders in this population in adulthood.

Even though stimulants are commonly recommended for the treatment of childhood ADHD, concerns that childhood use of prescribed stimulants may predispose an individual to a future substance use disorder are unsubstantiated (504). In fact, a recent meta-analysis of the literature indicated that childhood stimulant therapy lowers the risk of developing a concurrent alcohol or drug use disorder during adolescence and adulthood (505, 506).

Stimulant pharmacotherapy is effective for adolescent and adult ADHD (507) and may be effective for patients with a co-occurring substance use disorder (508–510); however, clinicians must carefully assess symptom improvement with stimulant treatment against the risk for misuse or diversion of prescribed stimulants. Prescription monitoring (e.g., limited dispensing, medication logs) and the use of long-acting stimulant preparations and standardized clinical symptom assessments (511, 512) are recommended. When there is concern about the safety of stimulant treatment in patients with ADHD and a substance use disorder, alternative ADHD pharmacotherapies without an abuse potential may be considered, such as atomoxetine, bupropion, and desipramine (513).

ADHD symptoms often interfere with a patient's adherence to substance use treatment, and therefore integrated psychosocial and pharmacotherapy treatment is recommended for patients with ADHD and a substance use disorder (501, 514). Although integrated psychosocial interventions for this population are recommended, research to support their use is limited. Expert consensus recommends providing patients with education about both disorders, encouraging their active participation in support groups, and modifying psychosocial treatments to facilitate learning (e.g., using brief structured sessions with written handouts) (288, 499).

f. Eating disorders

Epidemiological studies indicate an association between bulimia nervosa and substance use disorders, but not between anorexia nervosa and substance use disorders (515). Bulimia nervosa is more common among individuals with a substance use disorder than in the general population (515). Inpatient substance abuse treatment studies report that about 15% of women and 1% of men have an eating disorder; this group is more likely to abuse stimulants and less likely to use opioids than individuals without an eating disorder (515). In clinical samples, substance use disorders have been found to be common among patients with bulimia (about 23%) (516) and less frequent among those with anorexia nervosa (about 15%) (515). The types of agents abused by individuals with an eating disorder include diet pills, stimulants, laxatives, diuretics, emetics, and many other substances (515, 517). With chronic use, tolerance to the effects of and withdrawal from these medications can occur. Tobacco use and dependence are also common among individuals with bulimia and anorexia nervosa and may be linked with attempts to lose weight. Individuals with co-occurring bulimia and substance use disorders are more likely to be younger when they seek treatment for their bulimia nervosa and have an earlier onset of problem drinking compared with those individuals with bulimia nervosa only (516).

Integrated treatment may occur within psychiatric or substance use disorder treatment programs, and can combine traditional psychosocial treatments for substance use disorders with treatments for bulimia, including relapse prevention or CBT strategies (e.g., identifying automatic thoughts, thought restructuring, identifying cues and triggers for bingeing/purging and substance use). Substance abuse treatment programs may need to add nutritional consultation and education for these patients, help them set goals for an acceptable weight range, and observe them at and between meals for bingeing and/or purging behaviors (515, 518). The 12-

step recovery–oriented community groups for both disorders (such as AA and Overeaters Anonymous) can provide additional structure and support.

Medication strategies to treat bulimia or anorexia nervosa should follow the recommendations in APA's *Practice Guideline for the Treatment of Patients With Eating Disorders* (518). There are no controlled medication trials to guide treatment of bulimia nervosa co-occurring with a substance use disorder. Naltrexone may be worth considering for patients with co-occurring alcohol dependence and bulimia nervosa, given its clinical utility in bulimic patients (519, 520) and its established use with alcohol use disorders (see Sections IV.C.3.a and IX.B.3.a).

g. Personality disorders

Personality disorders and substance use disorders commonly co-occur, with an estimated 50%–60% of individuals with a substance use disorder having a co-occurring personality disorder (463, 521). Prevalence rates of borderline personality disorder (BPD) are approximately 30%–50% across inpatient, outpatient, and community samples of individuals with a substance use disorder (522). Antisocial personality disorder (ASPD) has a lifetime prevalence of 60% among injection drug users (523, 524), although there are recognized problems with the accuracy of an ASPD diagnosis in patients with a co-occurring substance use disorder due in part to drug-associated criminal behavior (525) and overlap with BPD (318). Establishing a personality disorder diagnosis in the context of a substance use disorder can be difficult and may be best done after a patient has achieved a prolonged period of abstinence from substance use. Because patients with a substance use disorder and BPD or ASPD have higher-risk behaviors and a higher suicide risk (303, 318, 526) as well as poorer treatment outcomes (527–532), improved instruments for assessing a co-occurring personality disorder in this context would help to identify high-risk patients who may require more intensive treatments.

Integrated treatments for this population initially focus on helping the therapist manage countertransference issues, develop a therapeutic alliance, and integrate existing behavioral therapy approaches for personality disorders into the substance use disorder treatment. Specific integrated psychosocial therapies that combine traditional substance use disorder treatment with the treatment of a personality disorder have been developed to address these co-occurring disorders (373, 374, 463). Although dialectical behavioral therapy has been shown to be effective for treating BPD with or without a co-occurring substance use disorder, it is not always effective in improving substance use outcomes (533), and there remains a need for improved integrated therapies for this high-risk population.

There have been few medication studies for co-occurring personality and substance use disorders. Medication recommendations in the APA's *Practice Guideline for the Treatment of Patients With Borderline Personality Disorder* (534) may be used to guide treatment. In some cases, medications for personality disorders are used episodically to treat specific symptoms. Benzodiazepines should be used with caution in patients with co-occurring personality and substance use disorders due to the risk of benzodiazepine abuse (535) and overdose and suicide attempts (536).

h. Pathological gambling

Individuals with a substance use disorder are vulnerable to other non-substance-related compulsive behaviors such as pathological gambling and compulsive sexual behaviors. Only pathological gambling is recognized as a DSM-IV-TR disorder. Individuals with a substance use disorder have about a four- to fivefold higher rate of pathological gambling when compared with the general population, and studies suggest that about 15% of substance abusers meet criteria for pathological gambling (537–539). The National Epidemiologic Survey on Alcohol and Related Conditions, a large nationally representative community study, reported that among adults with a lifetime history of pathological gambling, 73% have had a co-occurring alcohol use disorder, 38% have had a co-occurring drug use disorder, and 60% have had co-occurring nico-

tine dependence (540). It is likely that pathological gambling, though common, is underdiagnosed, because substance abuse or psychiatric treatment settings do not always screen for it (541). Individuals with pathological gambling and a substance use disorder are also at increased risk for engaging in unsafe sexual behaviors and having mood or anxiety problems, ADHD, ASPD, or legal problems (537, 539, 542, 543).

Integrated treatment programs rarely include pathological gambling treatment and generally do not provide Gamblers Anonymous meetings on-site (542, 544). However, integrated treatment could readily incorporate behavioral therapies for pathological gambling that are similar to traditional substance use disorder treatment, such as gambling relapse prevention strategies, social skills training, problem solving, and cognitive restructuring (544).

Medications that appear to help reduce the desire to gamble and gambling behaviors have not been examined in individuals with a co-occurring substance use disorder. Medications studied in pathological gambling alone include fluvoxamine (545–547) and naltrexone (548, 549). A large, multicenter, randomized, controlled trial of paroxetine plus psychosocial treatment failed to demonstrate a significant difference from placebo (550), and an open-label, flexible-dose study of sertraline also failed to demonstrate superiority to placebo (551). Lithium and valproate may be effective in the treatment of pathological gambling for those with bipolar disorder (552, 553). In general, medication trials for pathological gambling show a high early placebo rate; longer-duration studies may be needed to confirm the positive effects of medication.

3. Comorbid general medical disorders

Concurrent general medical conditions frequently complicate the treatment of substance use disorders. A full description of the medical problems associated with substance use disorders is beyond the scope of this practice guideline and has been provided elsewhere (554, 555).

Substance use causes a variety of health problems (Table 3), which vary depending on the substance used and its route of administration. These medical problems may be further complicated by the use of multiple substances and nutritional deficiencies that may accompany ongoing substance use. Many substance use disorder patients with a co-occurring medical disorder do not seek or receive adequate general medical care for a variety of reasons, including the chaotic and disorganized lifestyles often associated with substance abuse and these patients' lack of access to health care. Physicians may be reluctant to adequately treat the pain of individuals who have a painful medical condition but also a current or past substance use disorder (556). Thus, the substance abuse treatment encounter may be the first opportunity to address the general medical care needs of these patients.

At present, the medical risks associated with marijuana use are not well understood. Because it is likely that marijuana contains many of the same carcinogens as cigarettes, it is possible that lung cancer may occur in marijuana smokers, although there is no evidence to support this (557).

Substance use–related conditions such as hepatitis and tuberculosis and associated events such as motor vehicle accidents, falls, suicide, and homicide contribute to an increased risk of death and disability in the substance-using population. Tobacco-related medical disorders are a greater cause of mortality than alcohol-related medical disorders among individuals dependent on alcohol or other nonnicotine substances (558). This finding highlights the importance of assessing substance-abusing patients for tobacco use and recommending psychosocial and/or pharmacological intervention that will help them quit. Among individuals who inject drugs, infectious diseases are the most common cause of general medical comorbidity. Approximately 30%-40% of inner-city intravenous drug users test positive for HIV (559, 560), and depending on the treatment setting, as many as 30%–75% of substance use disorder treatment patients have been diagnosed with hepatitis C. Indeed, intravenous drug use accounts for 60% of new cases of hepatitis C and 25% of new HIV infections per year (561). Regardless of treatment setting, the adoption of universal precautions against body contamination by infectious agents is a necessary part of protecting staff and patients against the spread of HIV (562).

TABLE 3. Medical Disorders Associated With Specific Substances

Substance	Medical Disorders
Alcohol	*Gastrointestinal:* esophagitis, Mallory-Weiss tear, gastritis, peptic ulcer disease, fatty liver, alcohol-induced hepatitis, cirrhosis, acute or chronic pancreatitis *Cardiovascular:* hypertension, cardiomyopathy, coronary artery disease *Neurological:* Wernicke's encephalopathy, alcohol-related dementia, cerebellar degeneration, peripheral neuropathy, stroke, seizures *Hematological:* thrombocytopenia, anemia *Neoplastic:* cancers of the esophagus, liver, and pancreas *Other:* sexual dysfunction, sleep disorders, vitamin B deficiency, peripheral myopathy
Nicotine	*Cardiovascular:* coronary artery disease, vascular disease *Respiratory:* chronic obstructive pulmonary disease *Neoplastic:* cancers of the mouth, esophagus, and lung
Cocaine	*Cardiovascular:* ischemic heart disease, cardiac arrhythmias, cardiomyopathy, aortic dissection, myocardial infarction *Respiratory:* spontaneous pneumothorax, pneumomediastinum, bronchitis, pneumonitis and bronchospasm (when smoked) *Neurological:* seizures, stroke *Other:* sinusitis, nasal irritation, septal bleeding and perforation (with intranasal use), HIV and hepatitis (with intravenous use), weight loss and malnutrition
Opioids (when used intravenously)	*Gastrointestinal:* acute and chronic viral hepatitis *Cardiovascular:* endocarditis *Respiratory:* tuberculosis (which may be treatment resistant) *Neurological:* meningitis *Other:* cellulitis, abscesses, osteomyelitis, HIV

The risks of contracting sexually transmitted diseases commonly differ between the sexes. Among individuals with severe psychiatric disorders, men with hepatitis C have increased lifetime rates of drug-related risk behaviors (e.g., needle use, needle sharing, crack cocaine use), whereas women have higher lifetime rates of sexual risk behaviors (e.g., unprotected sex in exchange for drugs, money, or gifts; unprotected vaginal or anal sex) (563). All substance-using patients should be counseled about safe sex practices and taught specific interpersonal skills (e.g., assertiveness, negotiation) for discussing and requiring the use of safe sex practices with their partners. Gender-specific group treatments using educational/skills building approaches have been developed and are being studied (e.g., in the National Institute on Drug Abuse [NIDA] Clinical Trials Network studies to reduce HIV-related and sexually transmitted disease–related risk behaviors in patients in substance abuse treatment). Needle exchange programs and effective treatment of the substance use disorder and HIV or hepatitis C also reduce the spread of HIV and hepatitis C infection (561, 564).

When treating HIV-seropositive, opioid-dependent individuals with antiretrovirals and methadone, the physician needs to be aware of the clinically significant interactions between these two medications that can decrease the efficacy of antiviral medications and/or require methadone dose adjustments (565). It is recommended that individuals with hepatitis C receiving treatment with interferon be assessed for lifetime or current major depressive disorder because of the frequent development and/or exacerbation of depressive symptoms during treatment with interferon (566). All patients receiving interferon should be monitored for the develop-

ment of depression, and consideration should be given to initiating antidepressants and counseling. Guidelines for the psychiatric treatment of patients with HIV or AIDS are available in the APA's *Practice Guideline for the Treatment of Patients With HIV/AIDS* (567).

The rise of treatment-resistant tuberculosis among patients with a substance use disorder suggests the need to consider periodic tuberculosis screening for patients and staff who treat these patients, along with efforts to reduce the spread of tuberculosis in treatment environments. Supervised on-site chemoprophylaxis or treatment for tuberculosis within substance abuse treatment programs is also strongly recommended (568, 569).

4. Pregnancy

The treatment of substance use disorders is crucial in the pregnant woman because ongoing substance use during pregnancy has the following multiple implications for both the mother and the developing fetus:

1. *The health of the pregnant woman.* Pregnant women with a substance use disorder are at high risk for sexually transmitted diseases (e.g., HIV infection), hepatitis, anemia, tuberculosis, hypertension, and preeclampsia (570, 571). In addition, the presence of a substance use disorder may affect a woman's ability to maintain a healthy lifestyle, including proper nutrition and prenatal care.
2. *The course of the pregnancy.* Women with certain substance use disorders may be at greater-than-average risk for spontaneous abortions, preeclampsia, abruptio placentae, and early and prolonged labor (572–574), in addition to complications of other general medical conditions that may be attributable to the substance use (e.g., hypertension in cocaine users) (575).
3. *Fetal development.* Some abused substances, including nicotine, opioids, cocaine, and alcohol, are known to pass through the placenta and directly affect fetal metabolism and development (576–578). This may happen at any stage of development but is particularly likely during the third trimester, when maternal fetal blood flow and rates of placental transport are increased. Fetal concentrations of abused substances average 50%–100% of maternal blood levels and may be higher than maternal blood levels (579). The circulation of active metabolites is another source of fetal exposure to potentially toxic substances. The fetus may be at higher-than-average risk for birth defects, cardiovascular problems, impaired growth and development, prematurity, low birth weight, and stillbirth (573, 580–585). After delivery, the neonate may experience withdrawal from the substance, which may be difficult to recognize, particularly if the pediatrician is unaware of the mother's substance use disorder.
4. *Child development.* Some substances (e.g., alcohol) are associated with long-term negative effects on physical and cognitive development, as is seen in fetal alcohol spectrum disorders (586–588).
5. *Parenting behavior.* In addition to ongoing treatment for the disorder itself, mothers with a substance use disorder are frequently in need of education and training in parenting skills, social services, nutritional counseling, assistance in obtaining health and welfare entitlements, and other interventions aimed at reducing the likelihood of child abuse or neglect (589, 590). This is particularly true of women with co-occurring substance use and psychiatric disorders.

Goals for the treatment of pregnant, substance-using women include 1) providing appropriate treatment for the substance use disorder (e.g., methadone maintenance for opioid dependence and abstinence from other substances, including alcohol, cocaine, marijuana, and nicotine), 2) treating co-occurring medical or psychiatric disorders, 3) monitoring the safety of patient behaviors during pregnancy as well as during the postpartum period, 4) facilitating competent parenting behaviors, and 5) motivating the patient to remain abstinent after childbirth.

The optimal therapeutic approach is nonpunitive and maintains patient confidentiality. Education and counseling to help women make an informed decision about continuing or terminating a pregnancy should be provided. Women likely to return to a substance-abusing milieu should be counseled about long-term treatment options available in the community.

5. Gender-related factors

Information on the natural history, clinical presentation, physiology, and treatment of substance use disorders in women is limited. Although women are estimated to comprise 34% of all individuals with a substance use disorder other than nicotine dependence in the United States (591), psychosocial and financial barriers (e.g., lack of child care, lack of health insurance) prevent many women from seeking treatment (592). Another explanation for women's low utilization of substance use disorder treatment services may be women's perception of greater social stigma associated with their substance abuse (593–595). Once in treatment, women have been found to have a higher prevalence than men of primary co-occurring mood and anxiety disorders that require psychiatric care (593, 596). Many women with a substance use disorder have a history of physical and/or sexual abuse (both as children and as adults), which may also influence treatment planning, participation, and outcomes (597, 598). Female patients, particularly single mothers, may have more family responsibilities and may require more help with family-related problems. There is some evidence that tailoring the goals of treatment to meet the needs of women improves treatment outcomes for substance-using women (599, 600).

In terms of nicotine dependence, there is some evidence to suggest that women may smoke less for nicotine reinforcement and more for nonnicotine factors such as other sensory effects of smoke inhalation, conditioned responses to smoke stimuli, and secondary social reinforcement (601). It has also been suggested that women have more difficulties with smoking cessation than men, although recent studies have suggested that cessation rates are similar between the two sexes. There is some evidence that NRT is less effective in female smokers, but the evidence for this is not strong; any initial failures with NRT could be followed by nonnicotine therapies such as bupropion and clonidine (602). Two recent studies showed that women have improved rates of smoking cessation when treated with naltrexone in combination with either smoking cessation therapy alone (603) or NRT and psychosocial therapy (604). Naltrexone as an adjunctive treatment to NRT and/or smoking cessation therapy may also be a treatment option for women who have had initial failures with NRT, although more research is needed to support this. Factors that may lead to poorer outcomes in women include depressive symptoms, negative affect, and reduced social supports. Women also frequently cite the fear of weight gain or actual weight gain after smoking cessation as a reason for relapsing to smoking. Therefore, smoking cessation therapies for women should emphasize weight-management strategies.

Women may also experience more adverse physical outcomes from tobacco use. Women may be more sensitive to secondhand smoke than men (605), and studies indicate that women smokers are at increased risk for lung cancer of all histological types, even after controlling for the number of cigarettes smoked (606). Estrogen effects on carcinogenesis in the lung may account for this difference in women.

The prevalence of smokeless tobacco use in young men over the last several years has dramatically increased (607). This is particularly alarming given the high rates of oral cancer associated with smokeless tobacco use. Smokeless tobacco use should be taken into consideration in addition to cigarette, cigar, and pipe use during the assessment and treatment planning processes.

With regard to alcohol use, female-to-male ratios for alcohol abuse are highest in the younger age groups, suggesting more alcohol use among young women and a closure of the original gap in usage rates between the sexes (596, 608). Of notable concern is the poorer prognosis for medical sequelae of alcohol abuse and dependence in women. Alcohol-dependent women consume less alcohol than men yet progress to late stages of alcohol-related illness more rapidly

(609) and have a shorter time course to the initial development of alcohol-related medical morbidity than do men. Prevalence rates of alcohol-related cirrhosis of the liver and cardiomyopathy in women are twice that in men with alcohol abuse or dependence. Breast cancer and mortality are increased in women consuming more than two standard unit drinks per day (610). Alcohol-abusing women are also at higher risk for death when compared with same-sex, sober control populations (reviewed in Greenfield and O'Leary [611]).

One study of individuals with a substance use disorder in three outpatient treatment settings (methadone maintenance clinic, intensive outpatient program for cocaine dependence, and general outpatient substance abuse treatment clinic) showed that women with a substance use disorder reported significantly more cardiovascular, mood, nose/throat, CNS, skin, and gastrointestinal symptoms related to substance use than did men (612). This occurred despite the lack of differences between men and women in this sample in their preference for cocaine, alcohol, or opioid drugs. Women frequently initiate cocaine and opioid use in the context of a substance-using partner and tend to initiate use at a younger age than men (593, 613).

6. Age

a) Children and adolescents

An in-depth review of the evaluation and treatment of substance use disorders in children and adolescents is beyond the scope of this practice guideline. However, because an adult psychiatrist may be called on to evaluate children or adolescents with a substance use disorder, some general information and treatment principles are reviewed here. For more detailed information, the reader is referred to the American Academy of Child and Adolescent Psychiatry's *Practice Parameter for the Assessment and Treatment of Children and Adolescents With Substance Use Disorders* (614) and the Substance Abuse and Mental Health Services Administration (SAMHSA) recommendations for screening and assessing adolescents for substance use disorders (615–617).

Alcohol and other psychoactive substance use, abuse, and dependence in children and adolescents continue to present a serious public health problem in the United States. Alcohol and other substance use are among the leading causes of morbidity and mortality from motor vehicle accidents, suicidal behavior, violence, drowning, and unprotected sexual activity in this population (618).

Regional studies reveal that 7%-10% of adolescents are in need of treatment for substance use disorders (619). Children and adolescents are generally more likely to have abuse rather than dependence disorders and are less likely to appreciate the need for entering and remaining in treatment. Abuse is not necessarily a prodrome to dependence, and it may be developmentally limited in many adolescents. In addition, Pollock and Martin (620) demonstrated the importance of a new nosological entry in youth diagnoses entitled "orphan diagnoses" that includes subthreshold symptomatology of alcohol dependence (i.e., one or two symptoms only) but no abuse symptoms. A 3-year follow-up study demonstrated that this entity has a unique trajectory dissimilar to that of abuse and dependence.

Assessment and treatment of children and adolescents with a substance use disorder must take into account their psychosocial developmental levels and the possible role of their substance use disorder in impeding the successful attainment of developmental milestones, including a sense of autonomy, the ability to form interpersonal relationships, and general integration into society. The assessment should be multidimensional and address problems in several life domains, including psychiatric comorbidity, school or employment performance, family functioning, peer social relationships, legal status, and recreational activities (621).

Children reared in family environments in which other family members abuse or are dependent on alcohol or other substances are at higher risk for physical and sexual abuse, particularly when family members exhibit antisocial behaviors; these children may exhibit psychological and behavioral sequelae (including substance abuse) as a result (622, 623).

Most adolescents with substance use disorders also have one or more co-occurring psychiatric disorders, most often conduct disorder and/or major depression, although ADHD, anxiety disorders (including social phobia and PTSD), bipolar disorder, eating disorders, learning disabilities, and other axis II disorders are also common (624–626). Many adolescents with substance use disorders also have preexisting and concurrent impulsive, oppositional, self-injurious, and suicidal symptoms or syndromes (627). Treatment should also address these problems, with treatment of the substance use disorder(s) and coexisting psychiatric symptoms occurring simultaneously.

In general, the range of treatment modalities used with adults can be used with adolescents as well. These modalities include brief interventions, motivational enhancement strategies, cognitive-behavioral approaches, psychodynamic/interpersonal approaches (individual, group, and family), self-help groups (628), and medications when needed (629). Most adolescents are treated in outpatient settings, and treatment is often delivered in a group therapy format. Although research data establishing the efficacy of specific treatment modalities for adolescent substance use disorders are sparse, program outcomes for adolescents appear to be enhanced by the availability of treatment that is developmentally appropriate and peer oriented and includes educational, vocational, and recreational services. Corrective experiences in family interaction should be part of the treatment plan (628). Family therapy also appears to have benefit (241, 242, 630). Residential facilities are very effective in reducing substance use, but gains are lost when aftercare is not well coordinated (56).

The prevention of substance use and abuse is considered the primary intervention for schools and clinicians (631–633). At-risk children and adolescents include those with a substance-abusing parent and those living under deprived conditions (i.e., neglect and/or abuse). Educational programs describe the negative consequences of substance use and teach drug refusal and harm-reduction behavioral strategies. Life skills training is a substance use prevention curriculum (634) that focuses on teaching youths the skills necessary to avoid social pressures to experiment with smoking, drinking, and drug use. In addition to showing efficacy in white middle-class youth (634, 635), the effects of the life skills training approach has also been demonstrated to be beneficial in African American and Hispanic youth (636). Masterman and Kelly (637) noted that the empirical literature suggests that universal prevention programs may delay the onset of drinking among low-risk baseline abstainers (i.e., individuals who are not drinking at the baseline assessment and who would be predicted to be at low risk of developing an alcohol use disorder on the basis of multiple risk factors); however, not enough studies support the utility of such programs for at-risk adolescents. Furthermore, they argue that motivational interviewing within a harm-reduction framework is well suited to adolescents.

Interventions aimed at preventing smoking are similarly crucial, given that smoking rates among adolescents continue to rise, despite reductions in other age groups (638). Smoking in adolescents is often a marker of psychiatric problems such as another substance use disorder or depression. In adolescents who smoke, the motivation to quit is often low; many of these adolescents are nicotine dependent and will have difficulties stopping smoking without behavioral and pharmacological support. There have been relatively few studies of smoking cessation in adolescent smokers, and success rates with interventions such as brief motivational enhancement, nicotine patch, and bupropion appear to be very low, at approximately 20% by the end of treatment (639–641).

Two common assumptions concerning adolescent substance use that are unfounded should be mentioned. Supporting the findings of a recent meta-analysis (506), a 16-year prospective, controlled trial showed that the use of stimulant medication (e.g., methylphenidate) in adolescence to treat ADHD does not lead to increased substance use in adulthood (642). Furthermore, contrary to the common perception, cannabis withdrawal is highly prevalent in adolescents (643).

b) Elderly individuals

Substance use disorders in elderly individuals are often undiagnosed and undertreated (644, 645). Abuse of and dependence on prescribed medications, particularly benzodiazepines, sedative-hypnotic medications, and opioids, can contribute to excessive confusion and sedation in elderly patients, poor adherence with prescribed treatment regimens, and inadvertent overdose, particularly when these drugs are combined with alcohol (646–648). In addition, alcohol use disorders, whether an extension of a long-standing disorder or of later onset, are a major problem among elderly individuals, particularly those living alone (649–651). Alcohol-related cognitive impairment, co-occurring depressive disorder, dementia, poststroke syndromes, and other conditions are also common among elderly individuals and may impair their ability to obtain or adhere to treatment for a substance use disorder or other general medical or psychiatric disorder (652).

Although rates of smoking decline with age (by 15%–20%), elderly patients who do smoke should be encouraged to quit. Even in older smokers, smoking cessation can lead to health improvements, including improved quality and length of life. There are few published studies of smoking cessation in the elderly; however, clinical experience suggests that the use of NRT is a safe and effective option. However, caution should be used when prescribing bupropion to elderly individuals because of its potential hypertensive effects (653, 654). This agent should be considered as a second-line agent, as controlled studies have not been conducted in this population.

There is a paucity of empirical data on the treatment of substance use disorders in the elderly population; it is generally accepted that empirically supported treatments of adult substance use disorders can be effectively applied to the treatment of elderly patients. Some modifications, such as slowing the pace of therapy, placing follow-up outreach calls, and providing patients with written information, improve the effectiveness of some therapies. In a recent study of 250 elderly men screened for substance abuse from a VA outpatient population, predictors of patient engagement in substance abuse treatment included severity of substance use, co-occurrence of depression, healthy cognitive status, and higher educational achievement (655). A large multisite study (PRISM-E) has also shown that primary care patients screening positive for a substance use disorder prefer to be treated within the medical system, with integrated psychiatric and substance abuse services, rather than to have facilitated referral to outside treatment (31).

Studies of individuals with alcohol use disorders also suggest that the needs of older adults may be different from those of younger patients. Kofoed et al. (656) reported that VA patients age 54 years or older who received specialized services for elderly patients as part of a treatment program were four times more likely to complete the program and remained in treatment longer than those who received conventional services, although posttreatment relapse rates were comparable in the two groups.

7. Racial, ethnic, and cultural factors

Current research suggests poorer prognoses for ethnic and racial minorities in conventional treatment programs, although this may be accounted for by socioeconomic group differences (657–659). Although there is a paucity of research on the efficacy of culturally specific programming, treatment services that are culturally sensitive and address the special concerns of ethnic minority groups may improve acceptance of, adherence to, and, ultimately, the outcome of treatment. The training of staff to be sensitive to and incorporate culture-specific beliefs about healing and recovery should be part of a comprehensive treatment program that serves different minority and ethnic groups (660). For example, Native Americans and Alaskans may have a greater acceptance of treatment that incorporates the use of the Medicine Wheel (661, 662). Still, clinical judgment in determining what cultural-based modifications to treatment are appropriate is advised, because some ethnic groups have large heterogeneity (e.g., Latino/ Latina [663]); specialized cultural approaches (664) can be considered with a patient to determine whether or not the approach would be perceived as useful.

In terms of nicotine dependence, African Americans and Hispanics appear to be less likely to initiate smoking, tend to smoke in lower amounts, and have increased cotinine levels (due to slower metabolism of nicotine). When compared with whites, they appear less likely to become dependent but have less success in smoking cessation efforts (665–668). Recent studies suggest that the nicotine patch (669) and bupropion (670) are safe and effective treatments for African American smokers, but further study is needed.

8. Gay/lesbian/bisexual/transgender issues

Controversies in the literature exist about whether or not substance use rates are elevated in homosexual and bisexual populations. For example, earlier reports that lesbians are at higher risk than heterosexual women for alcohol-related disorders (671) have not been consistently replicated (672). Nonetheless, multiple studies do indicate increased rates of drug use among gay and bisexual sexually active men and lesbian women as compared with exclusively heterosexual men and women, with a prominence of cannabis and nicotine dependence for both homosexual men and lesbian women (673–675). In one undergraduate college student population, a higher incidence of drug use and smoking was found among gay and bisexual men and lesbian women as compared with heterosexual men and women (676). Among older gay, lesbian, and bisexual populations (ages 60–91 years), the incidence of alcohol abuse is greater for men than for women (677). Methodological issues of population sampling may confound interpretation of these findings. For example, in one community with a high concentration of gay and bisexual men, few differences were observed in drug use patterns among gay, bisexual, and heterosexual men (678). Furthermore, demographic variables other than sexual orientation influence the presence of substance abuse (679).

Because of concerns about increased risk and prevalence of substance use disorders in gay, lesbian, and bisexual populations, substance use disorder treatment programs frequently inquire about an individual's sexual orientation and whether or not the individual believes that his or her sexual orientation contributes in any way to the substance use. Special therapeutic strategies have been developed that target known regional associations between sexual orientation and substance abuse, such as a Los Angeles program for the treatment of male methamphetamine abusers who have sex with other men (680, 681). The rationale for this program was the discovery that this population has a high rate of HIV transmission. A similar concern over the higher prevalence of smoking among adolescent and adult gay, lesbian, and bisexual individuals has triggered the development of prevention and cessation programs for these populations (682, 683). SAMHSA published a statement in 2001 concerning the need to address substance abuse issues among gay, lesbian, bisexual, and transgender populations (684).

9. Family characteristics

Substance use disorders exact an enormous toll on family members. High levels of interpersonal conflict, domestic violence, inadequate parenting, child abuse and neglect, separation and divorce, financial and legal difficulties, and substance-related general medical problems (e.g., AIDS, tuberculosis), if present, can add to the family burden. In addition, children reared in family environments in which other family members abuse or are dependent on alcohol or other substances are also at increased risk of physical or sexual abuse (685).

Families who have one or more members with a substance use disorder often display a multigenerational pattern of transmission of both a substance use disorder and other frequently associated psychiatric disorders (e.g., ASPD, pathological gambling) (686, 687). The impact of maternal substance use on fetal development and childhood cognitive and emotional adjustment, coupled with the influence of genetically inherited risk factors (e.g., high genetic loading for alcoholism in the male population) and negative role models, plays a role in the development of substance use disorders across generational lines (688).

The substantial burden that having one or more members with a substance use disorder imposes on families and the impact of family interactions in perpetuating or ameliorating these problems affect the initiation of, perpetuation of, and patient's recovery from the substance use disorder; the patient's motivation and ability to adhere to treatment; and the patient's clinical course and outcome. These relationships, combined with the high prevalence of substance use disorders, co-occurring general medical and psychiatric disorders, psychosocial disability, and family burden make family screening and interventions extremely important (232, 236, 689, 690).

10. Social milieu and living environment

The patient's overall social milieu has an important impact on the development of and recovery from a substance use disorder. The social milieu shapes attitudes about the appropriate context for substance use (e.g., the difference between social drinking on family occasions and recreational drinking to achieve intoxication). Role models among one's family or peers influence the social and psychological context for substance use, the choice of substance, and the degree of control exerted over substance-using behaviors.

Once a pattern of dependence or abuse has developed, an individual's motivation and ability to adhere to treatment are influenced by the degree of support within his or her immediate peer group and social environment. Poor outcome is predicted by continued involvement with substance-using peer groups or family members as well as by residence in an environment in which substances are readily available. Addressing these issues is an important component of any treatment plan. Patients with high levels of psychosocial and environmental stressors need correspondingly high levels of community-based support or, in some cases, temporary relief from these stressors through treatment in a residential setting until the patient is able to develop specific relapse prevention strategies that can be applied in a community setting. Sexually active individuals should be educated about the prevalence and prevention of HIV infection and other sexually transmitted diseases (691).

Socioeconomic status may also play a role in the initiation and cessation of substance use. For example, smokers with lower education level, wages, and socioeconomic status are more likely to initiate smoking and less likely to quit; this may be due to less support for attempts to quit and less access to smoking cessation services. (692, 693).

▶ H. LEGAL AND CONFIDENTIALITY ISSUES

1.   Effect of legal pressure on treatment participation and outcome

Many patients with substance use disorders seek treatment in response to pressure from family members, employers, legal authorities, or other sources. Although being internally motivated for treatment is often regarded as a good prognostic sign, outcome studies of patients in therapeutic communities have shown that individuals who enter treatment under legal compulsion (e.g., as a condition of probation, to avoid incarceration) stay longer and do as well as comparable patients who enter treatment voluntarily (694, 695). The use of the opiate antagonist naltrexone has produced higher rates of adherence to court-mandated treatment by patients and physicians or other professionals who are at risk of losing their professional licenses should they fail to comply. Similar findings have been reported for professionals being treated for substance use disorders by means of contingency contracting approaches in which the contingency for nonadherence with treatment is being reported to a professional board of registration (696).

2.   Confidentiality and reporting of treatment information

To protect patients' privacy and encourage their entry into treatment, federal law and regulations mandate strict confidentiality for information about patients being treated for substance

use disorders (i.e., 42 U.S.C. Sections 290 dd-3 and ee-3; 42 C.F.R. Part 2). Disclosure of information from treatment records is prohibited unless the patient has given written consent, the disclosure is in response to a medical emergency, or there is a court order authorizing disclosure. Other times when patient confidentiality may be attenuated include disclosure needed to protect or warn third parties of potential harm by the patient, disclosure in response to a crime committed at the treatment program or against program staff, reporting of suspected child abuse or neglect, or, depending on the requirements of the local jurisdiction, reporting of suspected abuse of elderly individuals. Consequently, psychiatrists should be familiar with local and state reporting laws concerning the possible abuse and neglect of children, other dependents, or elderly individuals who may be at risk in the families of substance users.

Federal law generally does not make specific reference to the confidentiality of information pertaining to the HIV/AIDS status of a patient in substance abuse treatment, but there are many different state laws restricting disclosure of such status. The federal Health Insurance Portability and Accountability Act of 1996 has been particularly prominent in protecting the privacy of patients with a psychiatric disorder (697). Psychiatric disorders commonly co-occur with substance use disorders, and these patients are "doubly protected" by law.

3. Legal requirements for pharmacotherapy with opioids

Federal and state regulations govern the use of methadone, LAAM, and buprenorphine, the three opioids approved by the FDA for the treatment of opioid dependence. Programs that use these agents to treat opioid-dependent patients are registered with and accredited by the Center for Substance Abuse Treatment. The center holds opioid agonist treatment programs to a variety of accreditation standards that regulate issues such as admissions, record keeping, and the frequency of drug testing. In addition, individual states may also impose stricter licensing criteria for these programs.

In an effort to expand access beyond the highly regulated opioid agonist treatment programs, Congress passed the Drug Addiction Treatment Act of 2000, which allows "qualified physicians" in office-based practices to prescribe FDA-approved schedule III, IV, and V medications for the detoxification and maintenance of opioid dependence. Currently, sublingual buprenorphine and sublingual buprenorphine/naloxone are the only agents approved by the FDA for this purpose. Most physicians qualify by completing 8 hours of formal training and obtaining a special U.S. Drug Enforcement Agency number ("x" number). To obtain this number, physicians must have the capacity to refer patients for appropriate counseling and other ancillary services. Once qualified, physicians may treat patients in an individual or group practice with sublingual buprenorphine or sublingual buprenorphine/naloxone. As with all opioid agonist therapies, strict documentation of informed consent, qualification of the patient as being dependent on opioids with a history of relapse or medical risk, ongoing monitoring of efficacy, and evidence of abstinence or substance use through urine toxicology testing are required for safe prescribing. Physicians should also document the protection of children from accidental access to medication.

III. TREATMENT OF NICOTINE DEPENDENCE

▶ ### A. OVERVIEW

Smoking is common among individuals with other substance use and psychiatric disorders (698, 699). Although most psychiatrists do not offer comprehensive nicotine dependence

TABLE 4. Fagerström Test for Nicotine Dependence

Questions	Answers	Points
1. How many cigarettes a day do you smoke?	≤10	0
	11–20	1
	21–30	2
	≥31	3
2. Do you smoke more in the morning than during the day?	No	0
	Yes	1
3. How soon after you wake up do you smoke your first cigarette?	>60 min	0
	31–60 min	1
	6–30 min	2
	≤5 min	3
4. Which cigarette would you hate most to give up?	Not first	0
	First of day	1
5. Do you find it difficult to refrain from smoking in places where it is forbidden, for example, in church, at the library, in the cinema, etc.?	No	0
	Yes	1
6. Do you smoke if you are so ill that you are in bed most of the day?	No	0
	Yes	1

Source. Heatherton et al. (709). More information about the test is available in APA's *Handbook of Psychiatric Measures* (711).

treatment, the multiple negative health effects of tobacco use make it important for clinicians to identify tobacco smokers and smokeless tobacco users, provide motivational interventions to encourage patients to quit tobacco use, and be familiar with medications and psychosocial interventions that are effective in treating nicotine dependence. Although there have been several recent controlled studies of smoking cessation treatments among psychiatric patients (414, 700–705), most of these studies have been of limited sample size and primarily involved cohorts of patients with schizophrenia. Thus, much of what is recommended in this section is similar to other recommendations for psychiatric patients who smoke (173, 414, 698, 705) as well as being consistent with guidelines from the U.S. Public Health Service (706) for the treatment of smokers who do not have a current psychiatric disorder. It is also important to note that the treatment of nicotine dependence differs from that of other drug dependencies in the following ways: 1) treatment commonly uses pharmacotherapies (e.g., NRT, bupropion), with varying levels of behavioral treatment given to those willing to receive it; 2) a specific "quit date" when all tobacco use is to cease is set; 3) a nicotine-dependent individual generally does not experience substantial social/occupational dysfunction due to tobacco use; 4) there is less of a need for family involvement in such treatment; and 5) effective over-the-counter medication treatments are available for treating this dependence.

▶ **B.   ASSESSMENT**

In addition to the general aspects of assessment outlined in Section II.B, the patient's current level of tobacco use (e.g., number of cigarettes per day) and degree of nicotine dependence also need to be determined, because highly nicotine-dependent individuals are more likely to need more intensive therapy, especially pharmacotherapy. The Fagerström Test for Nicotine Dependence (Table 4) is widely used in treatment studies and has proven reliability and validity (707–710).

A score of <3 on this scale indicates that an individual has very low or no nicotine dependence, whereas a score of ≥6 suggests that an individual is highly dependent on nicotine (708). This scale

can also predict which smokers are likely to quit smoking and which may benefit from high-dose NRT (described in Section III.E.1). Nicotine dependence in smokeless tobacco users is common, and attempts have been made to measure dependence levels in this group as well (712).

Several other markers of nicotine dependence have been proposed, such as number of cigarettes per day, time to first cigarette (an item on the Fagerström test), cotinine levels, degree of withdrawal on last attempt, and number of unsuccessful attempts to quit. However, with the possible exception of time to first cigarette (713), these markers have yet to be shown to have significant treatment utility. DSM criteria for substance dependence (Table 2) also appear to be reliable and have prospective validity in diagnosing nicotine dependence (714).

As indicators of use, nicotine and cotinine levels can be measured in blood, saliva, and urine (105). Nicotine levels can reflect tobacco use over the last few hours, whereas the level of cotinine, a metabolite of nicotine, is sensitive to tobacco use in the last 7 days and offers a better measure of total daily nicotine exposure (105). It has been proposed that the measurement of cotinine levels be used to help guide nicotine replacement, but the utility of this strategy has not been well tested (173). An individual's carbon monoxide level is usually measured by breath and reflects smoking only over the last few hours (105). It has been suggested that the measurement of carbon monoxide is a means of motivating a patient to cease tobacco use or reinforcing abstinence (715), but the efficacy of this is unclear. The major benefit to using carbon monoxide levels as a marker is that it is easily measured and can be used to verify cessation of tobacco use when patients are using an NRT (105). Because smokers in nontreatment (or minimal treatment) settings are usually truthful about their smoking status and the number of cigarettes smoked per day (716), the described measures are not necessary for evaluating smoking cessation, although they show promise as helpful assessments.

Because 70% of smokers make more than one attempt to stop smoking (602), it is important and useful to inquire about and assess patient perceptions about prior attempts and past treatment adequacy. In addition to determining the patient's reasons for previous attempts to quit tobacco use and the amount of time he or she remained abstinent, it is important to assess the perceived cause of relapse. For example, was the relapse due to uncontrolled withdrawal symptoms, environmental stressors, alcohol use, negative or positive mood, psychiatric instability, or being around other smokers or tobacco users? Were there factors (e.g., fatigue, life disappointments, family or other social stressors) that undermined abstinence? What did the patient learn from prior failures? Past efforts to quit may also influence a patient's readiness and motivation to try quitting again. Thus, it is also important to understand the changes that a patient thinks need to occur before he or she can make another attempt to quit tobacco use, his or her fears about quitting, and the barriers to another attempt to quit.

For patients who have returned to tobacco use despite past efforts at treatment, a first consideration is the adequacy of prior treatment. For example: What was the duration of therapy? How many sessions of behavioral therapy were attended? What was the quality of the behavioral treatment in the last attempt to quit? What were the doses of gum or patch used? What was the level of adherence with the psychosocial or somatic therapy? It is also helpful to determine the patient's satisfaction with prior treatments. For example, did he or she believe that treatment was helpful? Did treatment experiences change his or her expectations of future treatment or its outcome?

The assessment of psychiatric patients in terms of cessation of tobacco use focuses on a number of other key points:

1. Is the patient motivated to quit using tobacco in the next month?
2. Are there any psychiatric reasons for concern about whether this is the best time for cessation? Is the patient about to undergo a new therapy? Is the patient presently in crisis? Is there a problem that is so pressing that time is better spent on this problem than on cessation of tobacco use?

3. What is the likelihood that cessation would worsen the non-nicotine-related psychiatric disorder?
4. Are there any signs or symptoms of other undiagnosed psychiatric or substance use disorders that might interfere with efforts to quit tobacco use?
5. What is the patient's ability to mobilize coping skills to deal with cessation?
6. What is the tobacco use status (e.g., never smoked, former smoker, current smoker) of others in the patient's household and among the patient's close friends?
7. What are the patient's treatment preferences and the basis for these preferences?

A discussion of the impact of these factors on the approach to treatment can be found in Section III.D, below.

▶ C. TREATMENT SETTINGS

With the exception of patients hospitalized for other reasons, treatment of nicotine dependence occurs on an outpatient basis. However, an inpatient model for smoking cessation has been described (717) and appears to produce high cessation rates, especially given the level of nicotine dependence among smokers who enroll. There are no controlled trials that substantiate this at the current time.

Regardless of the specific setting, treatment best occurs in a system that encourages cessation (33). This may be especially important to achieve on psychiatric inpatient units, as discussed below in Section III.G. The psychiatrist should also consider maintaining a smoke-free work site (33, 34).

▶ D. GENERAL APPROACH TO TREATMENT

As with treating other substance use disorders, the general goals in treating nicotine dependence include motivating and engaging an individual in treatment to reduce or preferably cease using tobacco. However, the general approach to treatment of nicotine dependence will depend on a number of factors, including the patient's psychiatric status, level of nicotine dependence, past treatment and efforts at quitting tobacco use, and current motivation for reducing or quitting tobacco use. This section discusses the general approach to nicotine dependence treatment; specific aspects of the pharmacotherapy and psychosocial treatments of nicotine dependence are discussed in Sections III.E and III.F, respectively.

Meta-analyses have found that the general techniques described below increase rates of quitting by a factor of 1.5–2.0 (718–721). Descriptive reviews of the skills and techniques critical to smoking interventions have also been published (33, 172, 722–728).

Research shows that 98% of tobacco use involves cigarettes, and most of the studies of treatments for nicotine dependence and smoking cessation have been in cigarette smokers (602). The available evidence suggests that other forms of tobacco use (e.g., pipe, cigars, smokeless tobacco) are becoming increasingly common (692). Although studies of treatment interventions are limited, pipe and cigar use are associated with higher rates of nicotine dependence because of their higher nicotine content. Thus, these other forms of nicotine use should also be taken into consideration in the assessment and treatment planning process.

1. Establishing and maintaining a therapeutic framework and alliance

Nicotine dependence is a chronic relapsing disorder; most smokers require five to seven attempts before they finally quit for good (729). Many patients do not realize that several attempts are often needed to stop smoking, and they will need to be remotivated to attempt to quit after a previous failure (33). Because of this, it is important to establish a therapeutic relationship so that the patient will accept treatment for subsequent attempts to quit, if necessary (33).

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Clinician advice for individuals attempting to quit tobacco use is best given in a nonjudgmental, empathic, and supportive manner (32, 33). No studies have been conducted to test whether confrontational interventions applied in treating other substance use disorders are useful with nicotine dependence. In patients with a present or past psychiatric disorder, it is important to convey the message that simply having a psychiatric disorder is not a reason not to make a quit attempt (725, 730).

2. Increasing readiness and motivation for smoking cessation

A patient's current motivation will determine what strategies should be used to enhance and support his or her readiness and attempts to quit smoking. Because many psychiatric patients are ambivalent about stopping smoking or are not ready to attempt to quit (731–733), nicotine dependence treatment will most often consist of enhancing their motivation and dealing with anticipated barriers to cessation (33).

Brief advice from a physician (using protocols similar to those recommended by the National Cancer Institute) to stop smoking typically doubles quit rates, from approximately 5% to 10% (718–721, 734, 735). Advice from nonphysicians is also effective (718, 721), and advice from multiple sources is more effective (718, 721). Thus, clear direct advice from the psychiatrist and other psychiatric personnel (e.g., nurses, social workers) to stop smoking is an essential initial therapeutic step that may increase patient readiness and motivation to try other therapies as needed.

Stages-of-change approaches and motivational enhancement models (32, 736) may help formalize interventions to enhance a patient's motivation. Such interventions will generally include providing information and feedback on the risks of smoking and reasons for quitting that are specific to the individual patient. The most common reasons for trying to stop smoking are to improve health and respond to social pressure (737). Revisiting the issue of smoking cessation at periodic intervals, especially with the occurrence of smoking-related medical conditions (e.g., bronchitis) or other special situations (e.g., pregnancy, living with a child with asthma), can sometimes motivate smokers to consider quitting (737–740). Documenting smoking status (as well as concurrent alcohol or other drug use) in the medical record may help facilitate such a follow-up.

3. Overcoming barriers to smoking cessation

Patients who smoke may express negative feelings or fears related to quitting that may serve as a barrier to their smoking cessation. The most common concerns are fear of weight gain, fear of withdrawal, and fear of failure (737). Women frequently cite the fear of weight gain or actual weight gain after quitting smoking as negative reinforcers contributing to smoking relapse. The exacerbation of psychiatric symptoms is likely to be an additional barrier for psychiatric patients (32). There is little evidence that smoking cessation can exacerbate psychiatric symptoms in patients diagnosed with schizophrenia or major depression whose symptoms are stabilized. However, any patient fears about withdrawal symptoms or a worsening of psychiatric problems may be dealt with by problem-solving approaches, increased monitoring by the clinician, behavioral therapy, or treatment with NRT, bupropion, or both.

Patients who smoke may also be uninformed and demoralized about their inability to change or may be defensive and resistant to change. Thus, it may be helpful for a clinician to clarify and legitimize patients' feelings, explore the reasons for their smoking, and offer expressions of support and respect. If feelings of demoralization are uncovered, they can be addressed by informing the patient that even smokers who are very committed to quitting may make several attempts to quit before they finally succeed. Patients who become chronically ambivalent about quitting may benefit from encouragement to take small steps toward their goal of quitting, such as reducing the number of cigarettes they smoke or trying to quit for just 24 hours.

The psychiatrist supports self-efficacy by identifying and praising past behavioral change and encouraging the use of strategies that were effective in the past.

Smoking by others in the household and close friends may also present a barrier to treatment. Whether and how others in the household and friends have supported or undermined a patient's prior attempts to quit should be evaluated. Conversely, social support is a major predictor of cessation (741). If others in the household are current smokers, it is useful to determine their willingness to quit at the same time as the patient or not to smoke in front of the patient.

4.   Eliciting patient preferences about treatment

Patients' treatment preferences and the reasons for those preferences should be elicited and considered when developing a treatment plan. For example, some patients may prefer to stop smoking on a certain date or may have strong likes or dislikes about pharmacotherapy, group therapy, or individual therapy. These factors will be important in setting a specific quit date as well as enhancing the patient's adherence to the treatment plan.

5.   Determining timing of smoking cessation

When and how cessation advice is best delivered must be determined by the patient's status; for example, smoking cessation is not likely to be successful when the patient is in crisis. The best time for cessation would appear to be when the patient is psychiatrically stable, there are no recent or planned changes in medications, and no urgent problems take precedence (730). On the other hand, admission to a smoke-free inpatient unit or integrating smoking cessation into other lifestyle changes that are a part of ongoing psychiatric treatment (e.g., during cessation of alcohol use) can sometimes motivate a patient to quit smoking. More immediate cessation is indicated if the patient has recently been diagnosed with a smoking-related medical disorder; individuals with such disorders generally have high success rates for quitting (737, 740). Whenever a smoking quit date is postponed, it is helpful to list smoking cessation as a goal on the master psychiatric treatment plan so that it can be addressed at a later time.

6.   Determining whether smoking cessation will be abrupt versus gradual

Most patients attempt and most clinicians recommend abrupt cessation of smoking rather than gradual reduction (742). Previous thinking has held that gradual reduction is less successful because patients appear to have difficulty achieving further reductions once they have cut down smoking to 5–10 cigarettes per day (173). On the other hand, most of the scientific data available suggest no difference in the outcomes of abrupt versus gradual cessation (173, 718, 719, 743); thus, patient preference to follow a gradual reduction strategy should be respected. A gradual approach may also be considered if the patient is historically uninterested or unable to quit smoking, as a significant and sustained reduction in smoking might still be achievable. Whether reductions in smoking are related to decreasing risk for smoking-related medical illnesses has not been clearly established (744, 745).

7.   Setting a quit date

Once the above factors have been addressed and the patient agrees to stop smoking, a specific quit date is set and a concrete discussion of cessation procedures occurs. In addition, the psychiatrist may give the patient written materials that provide suggestions for succeeding in quitting. Even if a gradual approach to smoking cessation is chosen, patients should generally be advised to set a date by which they will completely stop smoking and that they should not use NRT until they have stopped smoking. Because many patients relapse within the first few days of smoking cessation (746), it is important for the psychiatrist or the psychiatrist's staff to call or see the patient in the first 1–3 days after the quit date.

If the patient is not ready to make a commitment to a quit date, the psychiatrist should plan to readdress smoking at a later date, encourage the patient to reconsider, and offer to help if the patient changes his or her mind. In addition, the psychiatrist may give the patient written materials that are intended to motivate the patient to make a quit attempt or that give tips on how to successfully quit.

8. Developing a plan of psychosocial and pharmacological treatment

a) Initial approaches

In the general population, most smokers quit on their own or with minimal treatment (747); for those who are unable to stop with minimal intervention, many algorithms and guidelines recommend a stepped-care approach, with minimal intervention early on and more intensive intervention later in the course of treatment (140, 172, 748–750). At the same time, most smokers who quit on their own require several attempts before they succeed (750); thus any success later in the algorithm cannot be attributed to the specific treatment being given at that point. Just as important, early cessation of smoking can prevent much of the devastating consequences of smoking (751); thus, delaying delivery of a treatment known to be effective could allow a serious, irreversible consequence of smoking (e.g., acute myocardial infarction, lung cancer) to develop. Consequently, the availability of effective treatments for smoking cessation as well as the rarity of significant adverse effects of those treatments suggests that pharmacotherapy be offered to all patients who wish to stop smoking. Combining psychosocial and medication treatment generally produces the best outcomes; however, medications are effective even when no psychosocial treatment is provided.

b) Monitoring clinical status

After the first follow-up 1–3 days after the quit date (see Section III.D.7), additional follow-ups may be scheduled, depending on the patient's perceived need, history of cessation, and psychiatric history. Follow-up visits may also be needed to assess a medication blood level that might increase with cessation. Follow-up visits may also be needed to monitor side effects or plan tapering of antismoking medications.

At follow-up, the psychiatrist assesses whether the patient has smoked and, if so, the number of cigarettes smoked per day; the severity of the patient's withdrawal symptoms; the onset of any psychiatric symptoms; the patient's use of alcohol or other drugs; how the patient dealt with situations in which he or she felt a strong urge to smoke; medication side effects; and other relevant issues and then tailors treatment accordingly (33). Most but not all studies suggest that brief follow-ups (including telephone calls) increase quit rates (720, 721, 752–754).

(1) Identifying symptoms of withdrawal

Nicotine withdrawal symptoms typically begin a few hours after the patient has ceased smoking and include dysphoric or depressed mood; insomnia; irritability, frustration or anger; anxiety; difficulty concentrating; restlessness; decreased heart rate; and increased appetite or weight gain. Although most symptoms peak 24–48 hours after cessation, they last an average of 4 weeks, with hunger and craving for tobacco lasting 6 months or more in some individuals (755). The duration of nicotine withdrawal symptoms may be a more important determinant of smoking relapse than the severity of the symptoms (756). Smoking cessation can cause physiological problems such as slowing of electroencephalographic activity in the awake and sleep state, decreases in cortisol and catecholamine levels, and a decline in the patient's metabolic rate (757). The mean heart rate decline is about 8 bpm, and the mean weight gain is 2–3 kg (757).

Nicotine withdrawal can occur in association with all forms of tobacco use (cigarettes, chewing tobacco, snuff, pipes, cigars) as well as with NRTs (755, 757). The ability of these products to induce or maintain dependence and withdrawal increases with the rapidity of the absorption

of nicotine, the nicotine dose, and the availability of the product (758). Consequently, although symptom severity varies among patients (757), withdrawal is usually most severe with cigarette abstinence compared with abstinence from other forms of tobacco and nicotine medications (755, 757, 759).

(2) Identifying exacerbations of psychiatric symptoms

Patients with current or past psychiatric symptoms or disorders need particularly close monitoring in the first 14 days after smoking cessation because nicotine withdrawal symptoms such as anxiety, depression, increased rapid eye movement sleep, insomnia, irritability, restlessness, and weight gain can mimic, disguise, or aggravate the symptoms of other psychiatric disorders or side effects of medications. For example, when an alcohol-dependent individual who is also nicotine dependent is admitted to a smoke-free ward for alcohol detoxification, his or her anxiety, depression, difficulty concentrating, insomnia, irritability, and restlessness could be due to or aggravated by nicotine withdrawal. Although more studies support concurrent attempts to quit smoking and drinking, there is one study that suggests that relapse to alcohol is more likely with concurrent smoking cessation (38). There have been several prospective studies (760, 761) that have examined whether smoking cessation can exacerbate depressive (762–766) or psychotic (414, 702, 703, 767) symptoms in patients with major depression and schizophrenia, respectively; most of the available evidence suggests that this risk is low when patients' psychiatric symptoms are stabilized prior to the cessation attempt.

A patient's psychiatric status should also be monitored because blood levels of some psychiatric medications (e.g., those metabolized by the CYP 1A2 microsomal system, including clozapine, fluphenazine, haloperidol, oxazepam, desmethyldiazepam, clomipramine, nortriptyline, imipramine, desipramine, doxepin, and propranolol) may increase substantially within 3–6 weeks when patients taking such medications stop smoking, and these increases could worsen side effects or cause toxicity (414, 698, 760, 768, 769). This effect appears to be due not to nicotine but rather to the effects of benzopyrenes (tobacco carcinogens) and related compounds on the P450 system.

9. Providing education and enhancing adherence

Many patients do not realize their smoking may be a form of nicotine dependence (770). Key points to convey to patients include the following: 1) most smokers try to quit multiple times before they finally succeed, but with persistence, half of all smokers quit; 2) most smokers fail early on, but if the smoker is able to remain abstinent for 3 months, relapse is unlikely; 3) nicotine withdrawal can be relieved with NRT; 4) true withdrawal symptoms generally last 4 weeks or longer and may include dysphoric or depressed mood, insomnia, irritability, frustration or anger, anxiety, difficulty concentrating, restlessness, decreased heart rate, increased appetite, or weight gain (33).

To support a patient's adherence to treatment, it is important to deal with the patient's concerns about weight gain. Even though the health benefits of stopping smoking clearly outweigh the health risks of weight gain (771), fear of weight gain is common and is a major deterrent to smoking cessation, especially in women (772, 773). On average, smokers weigh 2–3 kg less than individuals who have never smoked, and when smokers stop smoking, they gain weight until they are similar in weight to those who have never smoked (771). Most smokers gain weight over the first few months after quitting smoking, but many later lose much or all of this weight. Women who are already trying to decrease their weight gain the most (773). However, smoking cessation-related weight gain does not cause a relapse to smoking (755). In fact, a concentrated effort to control weight gain by dieting during abstinence increases, not decreases, the chances of a relapse to smoking (774, 775). This may be because attempting to quit smoking and dieting at the same time is just too difficult. Clinicians can recommend that patients increase their physical activity and learn healthy eating strategies rather than diet or convince

patients to tolerate a moderate amount of weight gain over the first 3 months after smoking cessation and work on losing weight later (775). Nicotine gum, but not the nicotine patch, appears to delay weight gain and could be used to delay attempts to control weight until a relapse to smoking is less likely (776).

Alcohol use is a risk factor in most studies for relapsing to smoking (777); thus, it is recommended that patients who are attempting to quit smoking either diminish their alcohol intake or abstain from alcohol. Caffeine use typically does not change with smoking cessation (755), and it is unclear whether caffeine use is a risk factor for relapse (769). Smoking increases the metabolism of caffeine, and smoking cessation increases caffeine levels by 50%–60% (778). Because many of the symptoms of caffeine intoxication and nicotine withdrawal overlap (e.g., anxiety, insomnia, restlessness), reducing caffeine intake after smoking cessation might be helpful; however, the one study to test this hypothesis found caffeine does not increase the severity of tobacco withdrawal (778). In addition, abruptly stopping caffeine could induce a withdrawal syndrome of its own (779). In summary, with this contradictory evidence, patient preferences on whether to change caffeine intake should be respected.

Because smoking even one cigarette during a cessation attempt often portends a full-blown relapse (780), reports of any slips should prompt immediate planning around changes in behavioral therapy (e.g., discuss ways to avoid or cope with the situation that led to the slip) or changes in pharmacotherapy (e.g., increased dose, change in medication). If the patient has fully relapsed, the psychiatrist should praise the patient for even limited success. The patient and psychiatrist should then discuss what was learned with this quit attempt and when the patient would like to think about trying again. Most patients who relapse continue to be interested in stopping smoking; thus, the psychiatrist should discuss setting a time to reconsider another cessation attempt.

10. Determining approaches for patients who do not respond to initial treatment

When a patient does not respond to a trial of a known effective formal therapy (e.g., behavioral therapy, NRT, bupropion, a combination of these therapies), it is first important to determine if the treatment was adequately or inadequately implemented. If inadequately implemented, the therapy may be repeated with changes to ensure the fidelity to therapeutic steps, treatment adherence, and adequacy of treatment dose and duration.

If the treatment was both appropriate and adequately implemented, rescreening the patient for other co-occurring disorders is indicated, as other unrecognized substance use or psychiatric disorders can interfere with smoking cessation (698, 760, 781). The psychiatrist should also attempt to determine whether the relapse was related to withdrawal symptoms or other causes. If the patient has not previously been treated with NRT and the prior relapse appeared to be caused by withdrawal symptomatology, NRT is appropriate. If the patient has been adequately treated with NRT, the psychiatrist may consider bupropion and/or a different formulation or dose of NRT. If these approaches are also ineffective, the use of clonidine or nortriptyline could be considered.

Other NRT delivery systems can also be considered. Although its side effects can limit its acceptability to some patients, nicotine nasal spray produces a more bolus-like effect that might better relieve withdrawal symptoms and craving (782), especially in heavy smokers who report that they relapsed to smoking both for withdrawal relief and for the positive effects of nicotine and tobacco (e.g., liking, satisfaction). A nicotine inhaler has the added advantage of replicating the hand-to-mouth motor acts associated with smoking, which may further support its utility. A strategy of initially using nicotine nasal spray and then switching to a nicotine patch or concomitantly using nicotine nasal spray and patch has been proposed and received some empirical support from controlled studies (782a, 782b, 1563). The combination of a patch with a faster-acting NRT such as gum, lozenge, spray, or inhaler may have some rationale, as the patch provides a steady level of nicotine for withdrawal relief and the faster delivery systems address the positive aspects of smoking (satisfaction and liking).

If the patient has relapsed because of a stressful life event and has not previously been treated with behavioral therapy, this type of therapy should be considered. If the patient has already had behavioral therapy, two choices are available: 1) more intensive behavioral therapy or 2) behavioral therapy within a different content or format (e.g., group therapy, individual therapy, combined individual and group therapy, involvement of family members). Whether these treatments are effective for those who have not responded to prior behavioral therapy has not been studied. Sometimes it is difficult to distinguish withdrawal versus nonwithdrawal causes of relapse. Under such circumstances, the patient may be a candidate for combined pharmacological and behavioral therapy (783, 784).

The results of three small controlled studies of acupuncture are promising (785–787), but due to methodological limitations, they do not justify the use of acupuncture for treating nicotine dependence either alone or in combination with other treatments. Furthermore, a meta-analysis of 22 controlled studies suggests acupuncture lacks efficacy in promoting smoking cessation (788).

When the treating psychiatrist does not have the knowledge necessary to implement the treatments outlined herein, or if the strategies are administered and the patient is not able to quit smoking, the psychiatrist should consider referring the patient to someone who specializes in treating nicotine dependence.

▶ E. SOMATIC TREATMENTS

1. Nicotine replacement therapies

NRTs can be used as a first-line treatment approach for any individual who wishes to stop smoking. At present, there are five FDA-approved forms of NRT: patch, gum, lozenge, nasal spray, and inhaler. Because all are effective in alleviating withdrawal symptoms (789) and reducing smoking (790) in men and in women (791, 792), the choice of a specific NRT typically depends on patient preference and the NRT's route of administration and side effect profile (793). It is unclear what adjustments to NRTs are needed for pipe and cigar users; probably these therapies should be implemented according to the patient's nicotine dependence level as measured by the Fagerström Test (794). Using a combination of NRTs (790) or combining NRT with bupropion (795) or psychosocial therapies (790) may improve outcome.

The optimal duration of NRT is debatable (693). Although some individuals appear to require long-term use of NRT (e.g., ≥6 months), almost all eventually stop using such agents, and the development of dependence on these agents is rare (796, 797). Thus, patient preference should be the major determinant for the duration of an NRT.

Of the NRTs, many individuals find it easier to adhere to nicotine patch therapy. Typically, nicotine patch therapy will begin with a high-dose patch (21 or 22 mg); however, patients who smoke <15 cigarettes per day are candidates for starting with an intermediate-dose patch (e.g., 11 or 14 mg) or for using another form of NRT (798). Whether the 24- or 16-hour patch is better is debatable (71, 798). The 24-hour patch may better relieve morning craving but appears to cause insomnia in some patients (799, 800). Other common side effects are skin irritation (which can be diminished by rotating patch placement sites), nausea, and vivid dreams; however, patients usually develop tolerance to these side effects (790, 801). The recommended duration of nicotine patch therapy is 6–12 weeks, with a tapering of the patch dose over that period; longer durations of patch therapy have not been found to be more effective (790).

When nicotine gum or lozenges are used, scheduled dosing (e.g., one 2-mg lozenge or piece of gum every hour) rather than ad libitum dosing is often best. The 4-mg dose is recommended for heavy smokers (>25 cigarettes/day) or more nicotine-dependent smokers (790, 802, 803). The dose of nicotine replacement can be tapered over 6–12 weeks by decreasing the gum or lozenge dose (i.e., from 4 to 2 mg) and/or increasing the time between doses. Patients also ben-

efit from receiving instructions about proper use of these NRTs. With nicotine gum, patients should be instructed to chew one piece of gum very slowly until a slight tingling or distinctive taste is noted, at which time the gum should be placed ("parked") between the cheek and gum until the taste or tingling is almost gone. This process is then repeated over about 30 minutes for each piece of gum. Nicotine lozenges should be sucked on rather than bitten or chewed. Typical side effects of lozenges are minor but include nausea, heartburn, and mild throat or mouth irritation; side effects of the gum are jaw soreness or difficulty chewing (802, 804). In addition, the lozenge contains phenylalanine and should not be used by individuals with a history of phenylketonuria. With both the lozenge and the gum, it is important to avoid beverages other than water immediately before or during NRT use because associated pH changes can blunt nicotine absorption (804a).

Nicotine nasal spray and vapor inhaler systems provide faster delivery of nicotine than gum or lozenges, but still deliver nicotine more slowly and with lower peak nicotine levels than cigarettes. Nicotine nasal sprays produce droplets that average 1 mg per administration, and patients administer the spray to each nostril every 1–2 hours. Nicotine vapor inhalers are cartridges of nicotine that are placed inside hollow cigarette-like plastic rods and produce a nicotine vapor (0.013 mg/puff) when smokers puff on them (805, 806). The recommended dose is 6–16 cartridges daily, with the inhaler being used ad libitum for about 12 weeks. Short-term side effects from nicotine nasal spray include nasal and throat irritation, rhinitis, sneezing, coughing, and watering eyes in up to 75% of users (807–809), and nicotine inhaler use is most often associated with throat irritation or coughing in up to 50% of users (806, 810). When compared with other forms of NRTs, the nasal spray and inhaler may have somewhat higher rates of continued use for periods >6 months (782, 796, 811).

2. Bupropion

The antidepressant agent bupropion in the sustained-release formulation is a first-line pharmacological treatment for nicotine-dependent smokers who want to quit smoking. Bupropion appears to have comparable tolerability and effectiveness to NRTs (158–160, 795, 812) and is equally beneficial in men and women (813). The target dosage for individuals with nicotine dependence is 300 mg/day. The medication is initiated at 150 mg/day 7 days prior to the target quit date; after 3–4 days, dosing is increased to 300 mg/day (150 mg b.i.d.). Bupropion can also be used in combination with an NRT, although the evidence is mixed on the extent to which this improves outcomes (795).

The primary side effects associated with bupropion are headache, jitteriness, insomnia, and gastrointestinal symptoms (795). Caution is needed when prescribing bupropion to individuals with a history of seizures of any etiology, as seizures have also been observed with bupropion treatment. The use of bupropion, especially the short-acting preparation, is also discouraged in patients with a past, and particularly a current, diagnosis of an eating disorder (i.e., anorexia nervosa or bulimia nervosa) because of higher rates of seizures observed in initial studies of the medication (161). In other individuals, the rate of de novo seizures is low (<0.5%), and such seizures are predominantly observed when daily dosing exceeds 450 mg/day (795).

3. Other agents

There is also support for the use of nortriptyline and clonidine as treatments for nicotine dependence; however, given the number of other available treatments for which results are well validated, these should be viewed as second-line therapies. Nortriptyline may be particularly promising as a second-line nonnicotine pharmacotherapy, and its efficacy does not appear to depend on the presence of co-occurring depressive symptoms or major depressive disorder (795, 814). However, the side effects of nortriptyline are more prominent than those of NRTs or bupropion, and nortriptyline is also toxic in overdose amounts (455, 815–817). Clonidine

may also have some merit as a second-line agent (818), but its side effects may limit its use (819). Acupuncture (788) and other agents (e.g., naltrexone, mecamylamine, buspirone, monoamine oxidase inhibitors [MAOIs], SSRI antidepressants) (603, 795, 820–823) have also been studied, but their efficacy for smoking cessation has not been established.

▶ F. PSYCHOSOCIAL TREATMENTS

There is extensive evidence of the efficacy of psychosocial therapies for treating individuals with nicotine dependence, whether delivered in a group (824) or individual (825) format. These therapies are typically provided as a multimodal package of several specific treatments and aim to provide patients with the skills to quit smoking and avoid smoking in high-risk situations. Behavioral coping skills may include removing oneself from the situation, substituting other behaviors (e.g., walking, exercising), or using skills to manage triggers (e.g., assertiveness, refusal skills, time management). Cognitive coping skills may include identifying maladaptive thoughts, challenging them, and substituting more effective thought patterns to prevent a slip from becoming a relapse (e.g., not viewing the slip as a catastrophe). The 6-month quit rates for behavioral therapies in general are typically 20%–25%, or about twofold greater than quit rates with control conditions (824–828). A review of behavioral therapy studies also suggests that 1) more intensive behavioral therapies can produce better treatment outcomes versus low-intensity interventions (701, 703), and 2) behavioral therapies can augment smoking cessation outcomes with pharmacotherapies, including all NRTs and bupropion (414, 701, 703, 704).

1. Social support

Social support appears to be of benefit in encouraging an individual to quit smoking, whether it is measured according to the degree of support provided by a spouse or partner (829) or is provided in the form of a specific intervention (e.g., buddy system) (718, 826, 828, 830–833). Thus, social support is recommended as a treatment for smoking cessation.

2. Brief therapies

Brief therapies, such as behavioral supportive cessation counseling, may lead to enhanced rates of treatment retention or smoking cessation (639, 826, 828, 834–837). Such therapies can often be implemented successfully and economically in a broad range of health care settings. These therapies often incorporate elements of MET and encourage the patient to examine the reasons for and against quitting smoking. When brief interventions are used, patients are likely to have a greater number of quit attempts and a greater likelihood of success in smoking cessation (825, 826, 828).

3. Behavioral therapies

Behavioral therapies are recommended as a first-line treatment for smoking cessation, with a large database of over 100 controlled prospective studies on multimodal behavioral therapy supporting this recommendation (720, 734, 735, 826, 838). In most reviews and meta-analyses, 6-month quit rates with behavioral therapy are double those observed in control groups (824, 826, 828) and similar to long-term outcomes obtained with NRTs and bupropion. Specific types of behavioral therapy that have also been studied include contingency management, cue exposure, and "rapid smoking" aversion therapy; however, none of these are sufficiently well studied to support their use clinically.

4. Cognitive-behavioral therapies

Several controlled studies suggest that CBTs are effective for smoking cessation (700, 839, 840) and are possibly effective for smokers with comorbid depressive symptoms, major depression,

and alcohol and other substance use disorders (456, 459, 841–844). CBT may also help in addressing weight concerns associated with smoking cessation (840). However, the long-term effectiveness of CBT in this population has not been established.

5. Self-guided therapies

Self-help materials are designed to increase patients' motivation to quit smoking and teach them smoking cessation skills. In most (845–853) but not all (854, 855) studies, approaches such as community support groups, telephone counseling, written manuals, videos, and computer-generated, tailored self-help materials have shown promise in increasing smoking cessation rates. The use of multiple modes of therapy (e.g., written materials plus phone contact) (718, 720, 721, 856–859) and tailoring materials to the specific needs and concerns of each patient improves the effectiveness of self-help methods (736, 851, 860).

6. Other therapies

A number of other psychosocial therapies have been evaluated in a small number of clinical trials, with the results showing variable success. For example, some evidence suggests that exercise programs may help prevent a relapse to smoking in women (861, 862), whereas other studies do not (863, 864). However, based on the other health benefits of exercise, increased activity is encouraged in smokers attempting to quit or those who have recently quit smoking. There is also some support for the effectiveness of stimulus control techniques in reducing smoking urges, such as discarding cigarettes; removing ashtrays, lighters, and matches; avoiding smokers; and avoiding situations associated with smoking (718). However, these strategies are probably best used within the context of multicomponent therapies. Little evidence is available that would support the use of physiological feedback (i.e., giving immediate positive feedback on the benefits of smoking cessation such as decreasing carbon monoxide levels), gradual cessation (i.e., "nicotine fading"), or relaxation techniques (718). In addition, there is an insufficient number of studies of adequate research design regarding the use of 12-step programs, hypnosis, biofeedback, family therapy, IPT, or psychodynamic therapies for treating nicotine dependence, although clinical consensus suggests that such therapies may be useful in some patients.

▶ G. TREATMENT OF SMOKERS ON SMOKE-FREE WARDS

This section focuses on the treatment of psychiatric patients on smoke-free wards, a common issue confronted by psychiatrists. The principles described also apply to smokers on general medical wards seen in consultation and to smokers in smoke-free nonmedical settings, such as residential care settings. Controlled studies of treating nicotine withdrawal symptoms on psychiatric inpatient wards have not been published; thus, the recommendations below are based on treating withdrawal in outpatient settings (755, 757).

An inpatient stay may be an opportune time for initiating treatment for nicotine dependence because of the intensity of exposure to medical staff, diagnosis of medical conditions, and removal from usual smoking cues. It may therefore be helpful to include smoking cessation on the master treatment plan whenever relevant. As in other settings, smokers should be assessed for their readiness and motivation for change (32). Those considering quitting should be asked about their interest in using the temporary abstinence of the smoke-free unit as a beginning step toward permanently stopping smoking. In addition to the aspects of assessment discussed above in Section III.B, it may also be helpful to elicit from the patient any history of withdrawal symptoms in prior hospitalizations, withdrawal during prior voluntary quit attempts, or significant fear of withdrawal. An important but often neglected issue is the incorporation of NRTs and smoking cessation-related advice and aftercare into treatment plans on patient discharge (865).

1. System issues

Although many inpatient units have been concerned about implementing smoke-free units, most have found it less difficult than anticipated (34, 866, 867). Most (34, 866, 868–870) but not all (871) reports before and after the institution of smoke-free units indicate no increases in aggression, disruption, discharges against medical advice, use of medications or restraints, or admission refusals. However, a recent retrospective study on a smoke-free unit suggested that smokers may be more likely to be irritable or agitated than nonsmokers and that smokers who are not prescribed an NRT were more likely to be discharged against medical advice than other patients (865). Giving special off-ward privileges to allow patients to smoke or labeling off-ward passes as "smoking breaks" implicitly condones smoking (34, 866). In addition, there are risks in allowing some patients to have smoking breaks, such as patients with suicidal ideation or those with a history of eloping or exhibiting other problematic behavior on passes. Policies that provide breaks for smokers and nonsmokers on the same schedule may be preferable to policies that provide smokers with extra passes. Other recommendations for implementing a smoke-free unit are discussed in reviews (34, 866).

2. Patient education

Patients need to be educated about the rationale for a smoke-free unit; that is, that its purpose is not to force patients to stop smoking but to prevent secondhand smoke exposure to other patients and be consistent with the institution's goal to encourage healthy behaviors (34, 866). Patients should also be educated about the goal of smoking cessation treatment: to reduce withdrawal symptoms and, if patients are interested, to help them begin a cessation attempt (see Section III.D.9). Many patients are unaware of the valid symptoms of nicotine withdrawal and their time course; thus education about these can be helpful (34, 866).

3. Monitoring of symptoms

Although true for all individuals who stop smoking, it is particularly important to monitor patients in smoke-free inpatient settings for changes in psychiatric symptoms. Smoking cessation can worsen anxiety, insomnia, concentration, and weight gain, thereby confounding assessment and treatment of the patient's other psychiatric disorders (865). For example, because many alcohol-dependent patients smoke, it may not be clear whether their irritability, anxiety, insomnia, restlessness, difficulty concentrating, and depression are due to alcohol or nicotine withdrawal during alcohol detoxification on a smoke-free ward. Although nicotine withdrawal symptoms are thought to be milder than alcohol withdrawal symptoms, there is substantial person-to-person variability so that some alcohol-dependent smokers have nicotine withdrawal symptoms that are more severe than their alcohol withdrawal symptoms (872). When patients with schizophrenia are hospitalized and given higher doses of medications to treat acute psychosis, any increases in restlessness could be due to nicotine withdrawal rather than to neuroleptic-induced akathisia. Further confounding the source of the increased symptoms is the fact that smoking cessation can cause dramatic increases in blood levels of some medications (e.g., those metabolized by the CYP 1A2 microsomal system) (760, 873). In particular, clozapine levels can increase by up to 40% with smoking cessation (874).

4. Treatment of withdrawal symptoms

For some individuals, nicotine withdrawal during hospitalization is often not as severe as anticipated because of the absence of smoking cues, the distraction of the primary psychiatric problem, and the effects of medications. However, a recent retrospective study suggests there are clear benefits of providing NRTs to smokers on smoke-free inpatient psychiatric units (865), findings that are consistent with recommendations of the U.S. Agency for Healthcare Research and Quality's *A Clinical Practice Guideline for Treating Tobacco Use and Dependence*

(826) and with a meta-analysis of studies in nonpsychiatric inpatients (875). Thus, given the low risk of NRTs, prophylactic treatment with an NRT is suggested for all psychiatric inpatients who smoke. The advantages of nicotine gum in this context include the patient's ability to self-titrate the nicotine dose and stop using the gum immediately before intermittent smoking (e.g., during passes). In addition, many patients find that only a few pieces of gum per day are sufficient to prevent withdrawal symptoms (34, 866). The nicotine patch has the advantage of improved adherence and providing stable nicotine replacement. This may be especially advantageous in patients for whom a clinician is trying to differentiate nicotine withdrawal symptoms from psychiatric symptoms (873). For highly nicotine-dependent individuals, the use of more than one form of NRT (e.g., nicotine patch plus gum) may be helpful (865). A frequent question about prescribing NRT to patients on smoke-free units relates to those individuals who do not wish to stop smoking entirely and may use NRTs and cigarettes concurrently. However, such use of NRTs appears to be unlikely to produce significant adverse effects (865, 876–881). Bupropion can also be used in inpatient settings given its fixed dosing, easy monitoring, and efficacy in reducing signs and symptoms of the withdrawal syndrome (158).

Although the existing evidence does not show direct effects of psychosocial treatments on withdrawal symptoms, clinical experience suggests several strategies that may be useful for individuals in inpatient settings. Relaxation tapes can be used to alleviate anxiety. Anger can be averted by temporarily avoiding interactions; insomnia can be decreased by improving sleep hygiene; weight gain can be combated by increasing activity; and distraction and activities aimed at keeping busy can be used to get through craving episodes. Support groups for those going smoke free and support from family and significant others for going smoke free can be helpful as well.

▶ H. CLINICAL FEATURES INFLUENCING TREATMENT

1. Use of multiple substances

There is strong evidence that rates of smoking are much higher in patients with a substance use disorder than in the general population (347). For example, in the National Epidemiologic Survey on Alcohol and Related Conditions, the 12-month prevalence of nicotine dependence is 34.5% among individuals with any alcohol use disorder and 52.4% among individuals with any drug use disorder (347). Conversely, among subjects with nicotine dependence, the 12-month prevalence of an alcohol use disorder is 22.8% and that of a drug use disorder is 8.2%, rates that are 4.4- and 8.1-fold higher, respectively, those observed in non-nicotine-dependent individuals (347). A similar association between nicotine dependence and other substance use disorders has been observed in data from the National Comorbidity Study (349). In addition, the presence of alcohol or illicit drug use may be a negative predictor of smoking cessation treatment outcomes (698, 872). Although substance use and smoking are often concurrent and conditioned effects may be one important factor in determining the high rates of comorbidity and treatment failure, rates of smoking cessation among these individuals can still be substantial (349). In addition, many individuals with a substance use disorder express an interest in smoking cessation. In patients who do not express a current interest in quitting, motivational interventions should be used.

There is conflicting evidence about whether concurrent smoking cessation can increase, decrease, or affect at all the risk of relapse to alcohol (38), and it is also unclear whether cessation should be attempted concurrently or after initial abstinence from other substances. For these reasons, this decision may be guided by patient preference. In addition, there are few studies of pharmacotherapies in individuals with substance use disorders (705), but there is some evidence for the utility of NRT and behavioral approaches. The use of alcohol treatment-related

pharmacotherapies such as disulfiram or naltrexone might be considered in alcohol-dependent smokers, but there are no empirical studies to suggest the efficacy of these therapies in smoking cessation. In any case, such smoking cessation treatment should be made available in substance use disorder treatment programs.

2. Treatment in the presence of specific co-occurring psychiatric disorders

In the presence of a co-occurring psychiatric disorder, smoking cessation may be more difficult (349, 698, 760, 882). Psychiatric patients appear to have more withdrawal symptomatology when they stop smoking (414, 703, 767), probably as a function of their higher levels of nicotine dependence and smoking consumption. Cessation rates with NRTs (702, 703, 883) appear promising in patients with serious psychiatric disorders. Nicotine nasal spray and vapor inhaler systems provide faster delivery of nicotine, which may increase the rewarding effects of their use. However, no specific studies on these systems have been published in psychiatric patients, and the degree of difficulty of using these delivery systems and their side effects may limit their utility in this population (758, 884). Although many psychiatric patients smoke large numbers of cigarettes and inhale cigarette smoke deeply (885), using higher-than-normal doses of nicotine for heavier smokers has not been consistently shown to be more effective (790, 886). However, supplementation of the nicotine patch with ad libitum use of nicotine gum, lozenges, or inhaler appears helpful (887, 888). NRTs may also be considered as a way to reduce smoking even when patients do not have smoking cessation as a goal.

Initial psychosocial interventions for psychiatric patients may need to include higher intensities of behavioral therapy, because briefer psychosocial treatments are often unsuccessful (414, 702–704). There has been little study of behavioral therapies for smoking cessation in chronic psychiatric patients, although preliminary studies provide modest evidence that higher-intensity therapies may improve outcomes (701, 703). These studies have typically lacked a treatment as usual or minimal intervention controls, necessitating more controlled studies to establish the efficacy of these treatments. Combining higher-intensity behavioral treatments with an NRT or bupropion should be considered and has shown some modest success rates in preliminary studies (414, 701, 703, 704). In addition, psychiatric patients, including those who abuse or are dependent on substances, are more likely to benefit from behavioral therapy because of their high incidence of psychosocial problems, poor coping skills, and often, history of benefit from such therapy (730). When deciding between individual or group therapy, it is important to consider patient preference, as many psychiatric patients have experience with one or both kinds of psychotherapy. For some patients, both individual and group therapy may be indicated; for example, a specific problem that undermines cessation (e.g., a problem with assertiveness) might be addressed by individual therapy, whereas smoking cessation in general might be addressed in group therapy. Patients with low levels of coping skills or supports might also benefit from both individual and group behavioral therapy.

a) Schizophrenia

Rates of smoking in patients with schizophrenia are much higher (58%–88%) than in the general population (349, 889). The motivation to address smoking is often poor in these patients (882, 890), and thus motivational interventions as initial treatments are strongly suggested (891). In addition, the very low quit rates observed for these patients (349) suggest that more intense interventions are needed. Several controlled trials (414, 701–704) using combinations of higher-intensity behavioral support and pharmacotherapies (NRTs or bupropion) have shown modest short-term cessation rates, whereas one open-label trial of bupropion and supportive group therapy showed a decreased consumption of cigarettes in patients with schizophrenia (415). Concurrent alcohol and drug abuse in individuals with schizophrenia is high and can complicate cessation efforts; most studies have attempted cessation in patients whose drug use is in recovery and whose psychiatric symptoms are stable. Regular monitoring of an-

tipsychotic side effects and plasma concentrations may be needed because smoking cessation may increase levels of antipsychotic medications that are metabolized via the CYP 1A2 system (e.g., clozapine, olanzapine, fluphenazine, haloperidol) (see Section III.D.8.b.2). There is some evidence that in smokers with schizophrenia, the use of second-generation antipsychotic agents can either reduce smoking (e.g., clozapine) in those not wanting to quit (407) or facilitate cessation in those attempting to quit with the nicotine patch (703) or bupropion (414), but further studies of this effect are needed in larger samples.

b) Depressive disorders

Individuals with major depressive or dysthymic disorder also have high rates of smoking, with 12-month prevalence rates of about 30% (347). Similarly, about 17% of nicotine-dependent individuals have a 12-month prevalence of major depressive disorder (347), and 40% of smokers seeking treatment have a history of depression (760, 781). Current (765, 892, 893) and perhaps past (894) depression appears to be a negative predictor of treatment outcome during smoking cessation. Although pharmacotherapies for smoking cessation have not been carefully tested in patients with current (458) or past (456) major depression, antidepressants such as bupropion (158) or nortriptyline (456) should be strongly considered. In general, SSRIs do not appear to be efficacious in promoting smoking cessation (602, 795). Behavioral therapies such as CBT should also be considered for depressed smokers (456, 459, 893, 895), as these individuals are likely to fail with more minimal interventions. After a patient has quit smoking, his or her plasma levels of some antidepressants (e.g., TCAs) that are metabolized by CYP 1A2 may increase, necessitating close monitoring of levels and antidepressant side effects.

c) Other psychiatric disorders

Smoking rates in patients with a bipolar or anxiety disorder (e.g., PTSD, panic disorder), ADHD, or another substance use disorder (e.g., marijuana, opioids, cocaine) are also higher than in the general population, but there has been little study of factors associated with these patients' interest in quitting smoking or the efficacy of smoking cessation interventions with these patients (698, 699).

3. Comorbid general medical disorders

a) General issues

Nicotine dependence is the most frequent substance use disorder in all medical settings. In 2001, an estimated 46.2 million adults in the United States smoked cigarettes (896). A 2004 report of the U.S. Surgeon General (897) concluded that there is sufficient evidence to infer a causal relation between smoking and many medical conditions, including cancer and cardiovascular and respiratory diseases. Despite improved public awareness of its dangers, tobacco use continues to be the leading preventable cause of disease and death in the United States, leading to approximately 440,000 deaths per year (898). Because the duration of smoking is a substantial contributor to the associated harms from inhalation of tar and carbon monoxide, early intervention is important if smoking-related morbidity and mortality are to be prevented.

It is not surprising that smokers with psychiatric disorders have an increased risk for nicotine-related medical disorders because individuals with a psychiatric and/or a substance use disorder are two to three times more likely to be dependent on nicotine than the general population (347) and smokers with psychiatric disorders consume nearly half of all the cigarettes consumed in the United States (349). In addition, many of these individuals are obese, consume harmful levels of alcohol and salt, and do not exercise or undergo cholesterol screenings (899). As well as having increased medical comorbidity, smokers on psychiatric or other medications that are metabolized through CYP 1A2 will require higher medication doses compared with nonsmokers (414, 698, 760, 768, 769).

Environmental tobacco smoke (secondhand smoke) also contributes to increased morbidity and mortality and has been classified by the U.S. Environmental Protection Agency as a known cause of lung cancer in humans (group A carcinogen). Secondhand smoke is estimated by the agency to cause approximately 3,000 lung cancer deaths in nonsmokers each year (900). Given the high proportion of individuals with psychiatric disorders who smoke, those who reside or attend treatment programs with large numbers of other smokers may be at increased risk from environmental tobacco smoke.

b) Issues related to specific physical disorders

Cardiovascular disease, lung cancer, and chronic obstructive pulmonary disease are the most common causes of morbidity and mortality among smokers, making it important to screen smokers for the signs and symptoms of these conditions (751, 901). Among smokeless tobacco, cigar, and pipe users, mouth and upper airway cancers are the most common causes of tobacco-induced mortality, and users of these forms of tobacco should be screened for the presence of these diseases (751, 901).

With smoking-related physical disorders, the duration of smoking abstinence is directly related to decreases in risk within 5 years of cessation (902–906). Smoking cessation also leads to an improved quality of life. Because medical hospitalization, cancer diagnosis, impending surgery, or exacerbation of cardiorespiratory symptoms may motivate individuals to consider smoking cessation, treatment for nicotine dependence is particularly important at these junctures. Screening for other substance use is also indicated, as smokers with pulmonary problems may be highly dependent and have a comorbid alcohol use disorder.

In general, the treatments for nicotine dependence that are recommended for use in the general population are effective in patients with co-occurring general medical conditions. NRTs decrease acute symptoms of nicotine withdrawal and increase smoking cessation rates (839, 907–912) without appearing to have any increased risk of adverse outcomes (836, 876, 913–916). Bupropion also appears to be safe as well as effective in individuals with cardiovascular (917) and pulmonary disease (918). Behavioral interventions improve smoking cessation rates when administered alone (875, 919, 920), as a package of several behavioral interventions (836, 875, 920, 921), or in combination with an NRT (908, 911, 912); they appear particularly useful when delivered in more intensive formats (855, 875, 920) or in conjunction with a program of smoking cessation aftercare (836, 875, 920, 921).

4. Pregnancy

Pregnant women who smoke pose an immediate and considerable challenge, given the risks of smoking to the fetus (574, 922–928). Screening patients for their smoking status during pregnancy is essential, and biochemical measures may be more accurate than self-report measures in identifying those in need of intervention (929). The primary risk of smoking during pregnancy appears to be low-birth-weight infants. If a woman quits smoking by her third trimester, the risk of giving birth to a low-birth-weight infant is no greater than the risk to a nonsmoker (930–935).

There is good evidence that physician counseling about smoking during pregnancy is effective (936, 937). In addition, behavioral interventions may be preferred by many women (938, 939); thus, these interventions should be considered first-line treatments for pregnant smokers (939).

The evidence is mixed on the ability of NRTs to augment rates of smoking cessation in pregnant women compared with behavioral interventions alone (940, 941). Although there appears to be no increased risk for NRTs in pregnancy (930, 938), this has not been well studied. Nevertheless, the consensus suggests that any increase in risk that might occur with NRTs is likely to be less than the risk of ongoing smoking (942, 943). Intermittent forms of NRTs may be preferred over the nicotine patch as the former minimize nicotine exposure to the fetus (930). Al-

though there are no reports on the teratogenicity of bupropion, the decision to treat a pregnant woman with bupropion should include consideration of the potential benefits and risks to the woman and the fetus.

Regardless of the form of treatment used to augment smoking cessation in pregnant women, postpartum relapse rates are high (738, 929, 944, 945), suggesting a need for additional efforts at relapse prevention.

IV. TREATMENT OF ALCOHOL-RELATED DISORDERS

▶ A. OVERVIEW

The focus of this section is on the treatment of patients with alcohol dependence or abuse. However, treatment of these disorders may be complicated by episodes of intoxication and withdrawal, the treatment of which is discussed in Sections IV.C.1 and IV.C.2. Alcohol use disorders are common. In the National Epidemiologic Survey on Alcohol and Related Conditions, the 12-month prevalences were 4.65% for alcohol abuse and 3.61% for alcohol dependence (23), with corresponding 12-month prevalences in the National Comorbidity Study of 3.1% and 1.3%, respectively (946), and prevalences of lifetime disorder that were about five times the 12-month prevalences (947).

The course of alcohol use disorders is variable and frequently characterized by periods of remission and relapse. The first episode of alcohol intoxication is likely to occur in the mid-teens, and the age at onset of alcohol dependence peaks at ages 18–25 years (947, 948). The first evidence of withdrawal, if it occurs, is not likely to appear until many other aspects of dependence have developed. Although some individuals with alcohol dependence achieve long-term sobriety without active treatment, others need treatment to stop the cycles of remission and relapse (949).

The relation of alcohol dependence to alcohol abuse is also variable. In one study (950), only 30% of male subjects with alcohol abuse at baseline met criteria for alcohol dependence 4 years later; the other 70% either continued to meet criteria for alcohol abuse or saw their alcohol problems remit entirely.

The long-term goals of treatment for patients with an alcohol use disorder are identical to those for patients with any type of substance use disorder and include abstinence (or reduction in use and effects), relapse prevention, and rehabilitation. There is some controversy in the literature, however, regarding the possible benefits of striving for a reduction in alcohol intake, as opposed to total abstinence, for those who are unlikely to achieve the latter. A comprehensive review of the issue (951) concluded that a lower severity of pretreatment alcohol dependence and an individual's belief that he or she could control his or her drinking were associated with the individual's achieving controlled drinking after treatment. Interventions aimed at achieving moderate drinking have also been used with patients in the early stages of alcohol abuse (952, 953). Controlled drinking may be an acceptable outcome of treatment for a select group of patients when it is accompanied by substantial improvements in morbidity and psychosocial functioning. However, abstinence is the optimal goal that achieves the best long-term overall functioning (9).

Numerous studies (43, 954, 955) have documented positive outcomes among individuals who receive treatment for alcohol dependence; approximately 70% of all such patients manifest a reduction in the number of drinking days and improved health status within 6 months (43).

The majority of patients who are treated for an alcohol use disorder have at least one relapse episode during the first year after treatment. However, there is considerable evidence to show that most individuals with an alcohol use disorder drink less frequently and consume less alcohol after receiving treatment compared with before treatment (956–959). For example, patients typically report drinking heavily on 75% of the days during a 3-month period before treatment, whereas during posttreatment follow-ups, they report being abstinent on 70%–90% of the days and engage in heavy drinking on 5%–10% of the days (231).

Treatment has also been shown to bring about improvements in family functioning, marital satisfaction, and psychiatric impairments (43, 290, 960–963). Although improvements after treatment for alcohol dependence are at least in part attributable to nontreatment factors such as patient motivation (964), it is generally accepted that treatment does make a difference, at least in the short run.

▶ B. TREATMENT SETTINGS

The choice of treatment setting for an alcohol-dependent individual will be determined by the results of the initial medical and psychiatric evaluation (see also Section II.C). In addition, the optimal treatment setting and subsequent treatment outcome are likely to vary depending on the characteristics of the individual patient (965, 966).

Patients with alcohol withdrawal must be detoxified in a setting that provides for frequent clinical assessment and the provision of any necessary treatments (967). Some outpatient settings can accommodate these requirements and may be appropriate for patients deemed to be at low risk for a complicated withdrawal syndrome, with medical detoxification being accomplished using the medications described below (see Section IV.C.3). Postdetoxification treatment can also be successfully conducted outside of the hospital (e.g., in outpatient, day hospital, or partial hospitalization settings) for most patients with alcohol dependence or abuse (51, 956, 967). Intensive outpatient care involving frequent visits or conducted in a day hospital is generally preferable for the early phase of treatment. It is usually preferred that a significant other be available for travel to and from the treatment site, medication monitoring, symptom evaluation, support for abstinence, and communication with a responsible health care professional on behalf of the alcoholic patient. Relapse prevention medications should always be considered after detoxification. Currently available medications are naltrexone, disulfiram, and acamprosate (see Sections IV.C.3.a–c).

Patients who are unlikely to benefit from less intensive and less restrictive alternatives may need to be hospitalized at times during their treatment. In particular, those who have a history of withdrawal seizures or delirium tremens, whose documented history of very heavy alcohol use and high tolerance places them at risk for a complicated withdrawal syndrome, who are concurrently abusing other substances, who have a severe comorbid general medical or psychiatric disorder, or who repeatedly fail to cooperate with or benefit from outpatient detoxification are more likely to require a residential or hospital setting that can safely provide the necessary care. Patients in severe withdrawal (i.e., delirium tremens) always require treatment in a hospital setting. Patients who fail to achieve abstinence or who relapse frequently should also be given a trial of inpatient care. Under some circumstances, psychiatrically or socially unstable individuals may similarly benefit from the stabilization provided by a residential treatment setting.

Inpatient care should include medical detoxification and a program of rehabilitation. Although many inpatient and residential treatment programs have been traditionally organized around a treatment length of 28 days, empirical studies have not yet identified a specific optimal length of stay for the treatment of patients with an alcohol use disorder. Moreover, 28 days is a brief period in the natural history of a chronic disease.

Regardless of whether treatment for an alcohol use disorder begins in an inpatient or outpatient setting, the pivotal factor in successful treatment is engaging the patient in long-term outpatient relapse prevention with a duration measured in years rather than days. Patients should also be encouraged to participate in 12-step or other self-help group programs during outpatient rehabilitation.

▶ C. SOMATIC TREATMENTS

1. Treating intoxication states

In general, the acutely intoxicated patient requires reassurance and maintenance in a safe and monitored environment in which efforts are made to decrease external stimulation and provide orientation and reality testing. Adequate hydration and nutrition are also essential. Clinical assessment should follow the general guidelines described in Section II.B, giving particular emphasis to the patient's general medical and mental status, substance use history, and any associated social problems. Patients presenting with signs of intoxication should also be assessed for the possibility of recent use of other substances that could complicate their clinical course. Patients with a history of prolonged or heavy drinking or a history of withdrawal symptoms are at particular risk for medically complicated withdrawal syndromes and may require hospitalization.

2. Treating withdrawal syndromes

The treatment of alcohol withdrawal has two major goals: 1) help the patient achieve detoxification in a manner that is as safe and comfortable as possible and 2) enhance the patient's motivation for abstinence and recovery (968). According to DSM-IV-TR, the syndrome of mild to moderate alcohol withdrawal generally occurs within the first several hours after the cessation or reduction of heavy, prolonged ingestion of alcohol. It includes signs and symptoms such as gastrointestinal distress, anxiety, irritability, elevated blood pressure, tachycardia, and autonomic hyperactivity.

The syndrome of severe alcohol withdrawal, including delirium tremens, occurs especially within the first several days after cessation or reduction of heavy, prolonged ingestion of alcohol; the syndrome includes signs and symptoms such as clouding of consciousness, difficulty in sustaining attention, disorientation, generalized tonic-clonic seizures (grand mal) seizures, respiratory alkalosis, and fever (969–971). As described in DSM-IV-TR and elsewhere (972, 973), <5% of individuals with alcohol withdrawal develop severe symptoms and <3% develop grand mal seizures. In the past, the mortality rate for patients experiencing alcohol withdrawal delirium was as high as 20%; currently, it is closer to 1% because of improved diagnosis and medical treatment (972). The presence of a co-occurring medical disorder may also increase the likelihood of a complicated withdrawal syndrome (974–976). Because mounting evidence suggests that repeated episodes of alcohol withdrawal may lead to a worsening of future withdrawal episodes (a phenomenon known as the alcohol withdrawal kindling or sensitization effect), individuals with multiple previous withdrawals may require more aggressive treatment (977). To aid in identifying individuals at risk for severe alcohol withdrawal, a number of standardized instruments have been developed that assess and qualify the severity of withdrawal symptoms, with perhaps the most widely used being the Clinical Institute Withdrawal Assessment for Alcohol Scale, Revised (978, 979).

For approximately 67% of the patients with mild to moderate withdrawal symptoms, generalized support, reassurance, and frequent monitoring are sufficient treatment (980), although the effectiveness of supportive treatment for these patients relative to pharmacotherapy is not well established (981, 982). In one case-control study (981), 74% of hospitalized alcohol-dependent patients without a serious comorbid general medical problem responded to supportive treat-

ment for alcohol withdrawal. Consensus does suggest that thiamine be given routinely to all patients receiving treatment for a moderate to severe alcohol use disorder to treat or prevent common neurological sequelae of chronic alcohol use (983–986). In addition, patients in more severe withdrawal and those who develop hallucinations require pharmacological treatment.

The criteria for an ideal pharmacological agent to treat alcohol withdrawal include effectiveness in relieving symptoms and preventing seizures and delirium; a benign side effect profile, including safety in overdose; limited interactions with other medications; tolerability by those with comorbid medical conditions; tolerability by outpatients who may have cognitive impairment; and the ability to suppress drinking during and after alcohol withdrawal (987). Because no single agent or class of agents meets all of these criteria, a pharmacotherapeutic agent needs to be chosen according to the needs of the individual patient.

There are numerous reviews of the pharmacological treatment of moderate to severe withdrawal (987–993). The pharmacotherapy is directed toward reducing CNS irritability and restoring physiological homeostasis. This often requires the use of fluids, benzodiazepines, and, in selected cases, other medications (138, 987, 992, 994), as described below. In particular, benzodiazepines effectively reduce withdrawal severity and the incidence of seizures and delirium (991, 992). Carbamazepine, beta-blockers, and clonidine also diminish the severity of alcohol withdrawal symptoms but have not been proven to prevent delirium or seizures, which suggests that beta-blockers, clonidine, carbamazepine, and neuroleptics can be used adjunctively but not as monotherapy (992). In fact, there is some suggestion that protracted withdrawal symptoms and the relapse rate that occurs after successful detoxification may depend in part on what type of agent (benzodiazepine or anticonvulsant) is used during the acute detoxification period (977).

Additional factors need to be taken into consideration when choosing a medication in an outpatient detoxification setting. It is clear that benzodiazepines can cause sedation and, if used with alcohol, can be especially dangerous. Use of an anticonvulsant agent such as carbamazepine may be considered. Anticonvulsants, clonidine, and beta-blockers do not have the abuse potential of benzodiazepines and are not likely to be diverted for other uses. These factors may be particularly important in the outpatient detoxification of a person who abuses multiple substances.

a) Benzodiazepines

The use of benzodiazepines to control withdrawal symptoms takes advantage of the cross-tolerance between alcohol and this class of medication (972). A substantial body of evidence, including several meta-analyses (991, 992, 995), supports the use of benzodiazepines in the treatment of alcohol withdrawal.

The literature is less clear about specific benzodiazepines or a specific protocol for detoxification with benzodiazepines. Some authors suggest a single oral loading dose of 200–400 mg chlordiazepoxide or 20–40 mg diazepam, or as needed, may be used (996, 997). Orally administered chlordiazepoxide (50 mg every 2–4 hours), diazepam (10 mg every 2–4 hours), oxazepam (60 mg q2h), and lorazepam (1 mg q2h) are commonly used (982, 998). Another approach is to take the total dose necessary to suppress CNS irritability and autonomic hyperactivity in the first 24 hours (i.e., the stabilization dose) and give it in four divided doses the following day, after which the dose can usually be tapered over 3–5 days, with monitoring for reemergence of symptoms (999). For most patients, the equivalent of 600 mg/day of chlordiazepoxide is the maximum dosage, and many patients require less; a few, however, may require substantially more (1000). Patients in severe withdrawal and those with a history of withdrawal-related symptoms may require up to 10 days of treatment before benzodiazepines can be completely withdrawn. Benzodiazepine administration should be discontinued once detoxification is completed. Multiple randomized, controlled trials demonstrate the use of less medication as well as shorter duration of treatment in symptom-triggered detoxification protocols (998, 1001–1003).

For patients who have severe hepatic disease, are elderly, or have delirium, dementia, or another cognitive disorder, short-acting benzodiazepines such as oxazepam or lorazepam (1004) are preferred by some clinicians and appear to be efficacious (1005). Oxazepam and lorazepam do not require multistep biotransformation; they are metabolized by phase II enzymes (glucuronidation) that are not as affected by alcohol-related hepatitis. Glucuronidation is preserved even in severe liver disease and cirrhosis (1006, 1007), making these medications safer choices for such patients. Lorazepam also has the advantage of being able to be administered parenterally. However, because of their brief half-lives, the short-acting benzodiazepines need to be given more frequently (1008–1011).

b) Adrenergic agonists and antagonists

Beta-adrenergic antagonists (e.g., propranolol, 10 mg p.o. q6h) have been used to reduce signs of autonomic nervous system hyperactivity (e.g., tremor, tachycardia, elevated blood pressure, diaphoresis) and, at higher doses, arrhythmias (1012–1014). Atenolol has been used for a similar purpose, usually in combination with benzodiazepines (1015), thus allowing the use of lower doses of benzodiazepines and thereby reducing the sedation and cognitive impairment often associated with benzodiazepine use. Clonidine, an α-adrenergic agonist (0.5 mg p.o. b.i.d. or t.i.d.) has been shown to reduce tremor, heart rate, and blood pressure (1016, 1017). However, the use of beta-blockers or clonidine alone for the treatment of alcohol withdrawal is not recommended because of their lack of efficacy in preventing seizures (992).

c) Anticonvulsants

The use of anticonvulsants as a treatment for acute alcohol withdrawal has been investigated in several studies (977, 994, 1018–1020) and considered in two meta-analyses (991, 992) and a review (987). Anticonvulsants and benzodiazepines appear to have comparable efficacy in preventing seizures during alcohol withdrawal (995); however, the prophylactic use of anticonvulsants such as phenytoin is not generally recommended (1005, 1021–1023) except in individuals with a co-occurring seizure disorder who have stopped their anticonvulsant medications while drinking (1024). Other withdrawal symptoms may also be diminished by anticonvulsants (992, 994, 1018, 1020), particularly in patients with mild to moderate withdrawal, although the evidence for this is mixed (987) and sample sizes of studies considering this usage have generally been small, making meta-analysis problematic (1025). Carbamazepine (600–800 mg/day for the first 48 hours; then tapered by 200 mg/day) has also been demonstrated to be effective in preventing withdrawal-related seizures, although its tendency to lower white blood cell counts in some patients may pose an added risk of infection (1026–1030). Although the evidence for the use of oxcarbazepine is sparse, this medication may be useful as an alternative to carbamazepine (1031). Divalproex sodium at a dosage of 500 mg t.i.d. (994) and intramuscular magnesium sulfate (1032) have also been used for preventing withdrawal seizures. Barbiturates (e.g., pentobarbital, phenobarbital, secobarbital) may be useful in reducing withdrawal symptoms in patients whose symptoms are refractory to benzodiazepines (1033). However, more recent reviews indicate that well-controlled studies of phenobarbital are rare and do not recommend phenobarbital for routine treatment of alcohol withdrawal (987).

d) Antipsychotic agents

For patients manifesting delirium, delusions, or hallucinations, antipsychotic agents, particularly haloperidol (0.5–2.0 mg i.m. q2h, as needed) are recommended. Because antipsychotic agents are not effective for treating the underlying withdrawal state (992), they should be used as an adjunct to benzodiazepines. Most patients will require <10 mg of haloperidol every 24 hours, although some patients may require considerably more.

e) Intravenous ethanol

Although some hospitals maintain oral and intravenous ethanol in their formularies to treat alcohol withdrawal syndromes, there is no clear evidence for the effectiveness of ethanol in this application. Given the published evidence of intravenous or oral benzodiazepine treatment for minor and major abstinence syndromes and the lack of any controlled trials comparing the use of intravenous benzodiazepines such as chlordiazepoxide with intravenous ethanol, the use of intravenous ethanol is not supported by the current published data (1034, 1035).

3. Medications to treat alcohol abuse and dependence

a) Naltrexone

Naltrexone, an opiate receptor antagonist, is thought to act by preventing the opiate receptor–mediated euphoric and rewarding effects of alcohol, diminishing the rewarding aspects of alcohol-induced dopamine release, and blunting the subsequent craving for alcohol. Naltrexone is one of the most widely studied medications for the treatment of alcohol dependence. Meta-analyses have found it to be more effective than placebo in promoting abstinence, reducing heavy drinking days, and decreasing rates of relapse (152–154, 1036). Depending on the study and outcome measure used, naltrexone is associated with small to moderate benefits (e.g., with effect sizes of 0.1–0.5 and/or relative risk decreases of 10%–14%). In addition, individual responsiveness to naltrexone varies, with some evidence that a family history of alcoholism and high levels of craving may predict better naltrexone response.

Some single-site and small multisite trials from several countries have shown therapeutic benefits of oral naltrexone (187, 954, 1037–1041), whereas other larger multisite studies have not (1042, 1043). Long-acting injectable naltrexone also appears to be efficacious (1044). In a number of these studies, the type and amount of concomitant psychosocial interventions may confound the interpretation of the study findings (1042, 1043). Several studies have indicated that naltrexone works best when combined with a relapse prevention approach, such as coping skills or CBT (187, 1038, 1039, 1041). Conversely, when more severely dependent subjects have been studied without concomitant relapse prevention interventions, the efficacy of naltrexone has been less robust (1045) or nonexistent (1043).

With the initiation of naltrexone therapy, patients taking opioids may experience withdrawal symptoms; therefore, before starting naltrexone, patients should be opioid free for at least 5 days after the last dose of a short-acting opioid such as heroin or 7 days after the last dose of a longer-acting opioid such as methadone (see Section VII.C.1.c). A urine toxicology screen for opiate medication may be indicated before naltrexone therapy is initiated. In non-opioid-abusing patients, the 50-mg dose of naltrexone used in most studies has been associated with mild and transient side effects, including CNS-related symptoms (headache, fatigue, dysphoria) and gastrointestinal problems (nausea, vomiting, abdominal pain). Similar side effects are reported with the long-acting injectable naltrexone and are more prominent in doses of 380 vs. 190 mg i.m. per month (1044). In addition, injection site pain was noted in about 10% of patients (1044).

Although significant hepatoxicity has been reported with naltrexone, this side effect is rare at the usual doses. Moreover, liver function may improve in naltrexone-treated patients as a result of decreased drinking (1046). Hepatoxicity may be more likely in morbidly obese individuals or at doses higher than those normally used in clinical treatment (>100 mg/day). Hepatoxicity resulting from an interaction between nonsteroidal anti-inflammatory drugs (NSAIDs) and high-dose naltrexone has also been described (1047); clinicians should use high doses of naltrexone cautiously and warn patients accordingly. In addition, because naltrexone is an opioid antagonist, it would be inappropriate for patients requiring opioid analgesics. The

naltrexone-treated patient should carry a card explaining these issues and provide it to health care personnel in an emergency.

b) Disulfiram

Treatment with the aversive agent disulfiram (usually 250 mg/day, range 125–500 mg/day) is aimed at motivating abstinent alcoholic individuals to resist alcohol consumption. When aldehyde dehydrogenase is inhibited by disulfiram (151), alcohol consumption causes toxic levels of acetaldehyde to accumulate, which in turn is associated with a host of unpleasant and potentially dangerous signs and symptoms, including a sensation of heat in the face and neck, headache, flushing, nausea, vomiting, hypotension, and anxiety (148–150). Chest pain, seizures, liver dysfunction, respiratory depression, cardiac arrhythmias, myocardial infarction, and death have also been reported. The purpose of disulfiram is not to make the patient ill but to prevent a patient from drinking impulsively because he or she knows that illness will result from drinking while he or she is taking disulfiram. However, disulfiram is only effective to the degree that an alcohol-using individual adheres to taking it as prescribed. Methods to improve adherence include behavioral contracting between an alcohol-dependent individual and his or her spouse and other forms of monitored administration with set contingencies.

Controlled trials have not demonstrated any advantage of disulfiram over placebo in achieving total abstinence, delaying relapse, or improving employment status or social stability (1048, 1049), and a meta-analysis showed only some diminution in drinking with disulfiram (1036). However, a large VA multisite cooperative study did find that patients receiving 250 mg of disulfiram reported significantly fewer drinking days than those who either received no disulfiram or 1 mg of disulfiram (150). Moreover, some clinicians believe that this medication, when combined with other therapeutic interventions, has some benefit for selected individuals who remain employed and socially stable (150, 1048, 1050–1052). Patients who are intelligent, motivated, and not impulsive and whose drinking is often triggered by unanticipated internal or external cues that increase alcohol craving are the best candidates for disulfiram treatment. Treatment effectiveness is enhanced when adherence is encouraged through frequent behavioral monitoring (e.g., breath tests), group support for remaining abstinent (e.g., group therapy, AA) (1053), contingency contracting, or, where feasible, supervised administration of disulfiram (1054, 1055).

Disulfiram should never be used without the patient's knowledge and consent; understanding and explaining disulfiram's toxic or potentially lethal effects to patients is a prerequisite for its use (1056–1058). Patients taking disulfiram must be advised to avoid all forms of ethanol (including, for example, that found in some cough syrups). Disulfiram requires hepatic metabolism to convert it into an active medication. A metabolite of disulfiram is an inhibitor of CYP 450 3A4 (1059) and can interfere with the metabolism of a variety of psychotropic and other medications that are substrates for CYP 450 3A4. In addition to its aversive effects after the ingestion of alcohol, disulfiram can cause a variety of adverse effects that are rare but potentially severe, including neuropathies and hepatotoxicity. Thus, it should be used cautiously in patients with moderate to severe hepatic dysfunction, peripheral neuropathies, renal failure, and cardiac disease (1048). A patient who is impulsive, has poor judgment, or has a severe co-occurring psychiatric disorder (e.g., schizophrenia, bipolar disorder) that makes him or her unreliable or self-destructive (149, 1060) may also be a poor candidate for disulfiram treatment. Moreover, disulfiram is eliminated from the body slowly. Ingesting alcohol even 1–2 weeks after the last dose of disulfiram could cause an alcohol-disulfiram reaction (1061).

c) Acamprosate

In 2004 the FDA approved a new medication, acamprosate, for the treatment of alcohol dependence. The approval was based primarily on data derived from studies done in Europe (reviewed in 1062, 1063). Although the neuropharmacological action of acamprosate is not

completely known, researchers do know that it is an amino acid derivative of taurine that is thought to work at brain glutamate receptor sites and stabilize glutamatergic function (155). As such, it has been hypothesized that it might normalize an aberrant glutamate system present during early abstinence that may be the basis of protracted withdrawal and early abstinence craving (1064).

Studies in Europe have evaluated patients who have generally started on the medication while in a hospitalized setting and who were abstinent for at least 7–10 days before taking the medication; the results of those studies showed that an increased number of patients maintain abstinence. Those who relapsed had more abstinent time before their first drinking day and also more overall abstinent days during a year or more of treatment (1062, 1063, 1065, 1066). In contrast, a multisite trial completed in the United States did not find acamprosate to be effective in a primary intent-to-treat analysis but did find that when subjects' motivation to maintain abstinence and adhere to medication treatment was taken into account, acamprosate was more effective than placebo in increasing the number of abstinent days (1067). The U.S. trial included outpatients who had a varied number of abstinent days prior to medication initiation, but, in general, the overall pretreatment abstinent time was much shorter than that in the European trials. Also, subjects in the U.S. trial received a standardized medical management type of counseling, whereas the European studies generally used varied traditional psychosocial alcohol treatment approaches focusing on the maintenance of abstinence. It would appear that, although not specifically studied, a number of days (perhaps 7 or more) of abstinence prior to starting acamprosate might be needed for acamprosate to be most effective.

There is also some evidence that acamprosate and naltrexone can be given together, but the benefit of doing so has not been clearly established (954, 1068). The COMBINE Study, a multisite trial supported by the National Institute on Alcohol Abuse and Alcoholism is in the process of further assessing the efficacy of acamprosate alone and in combination with naltrexone with and without a specialist-delivered behavioral intervention (1069, 1070). Acamprosate has also been studied in combination with disulfiram and has shown an apparent improvement in efficacy (1071).

At a dosage of two 333-mg pills t.i.d. (total dose of 1,998 mg), which is an approved dose in the United States, acamprosate is well tolerated, with generally self-limited and symptomatically treated diarrhea being the main adverse effect. Because acamprosate is excreted by the kidneys and not metabolized by the liver, caution must be taken with patients who have renal impairment (1072). However, liver disease should not affect its metabolism or blood level concentrations. Acamprosate has minimal if any negative interaction with alcohol so that it is expected to be generally safe in active or relapsed drinkers.

d) Medications acting on the serotonin system

SSRIs have been used in the treatment of alcoholism to directly affect alcohol consumption, with the goal of reducing drinking or promoting abstinence. SSRIs also may reduce psychiatric symptoms or syndromes (e.g., anxiety, depression) that might influence drinking behavior.

In addition to evidence that serotonin modulates the behavioral effects of alcohol (479, 1073–1075), several randomized, double-blind, placebo-controlled human studies with nondepressed heavy drinkers found that SSRIs reduce short-term alcohol consumption by 15%– 20% (1076, 1077). However, subsequent studies in patients diagnosed with alcohol dependence have been less consistent (1078–1080) and suggest that SSRIs may worsen drinking behaviors in some individuals. The use of SSRIs in the treatment of alcohol dependence is similar to their use in other disorders (430), although gastrointestinal side effects may be more prominent in alcohol users.

TCAs also have nonselective effects on serotonin reuptake and have been used to treat depression associated with alcohol use disorders with equivocal results (138). However, two studies showed improved mood and reduced alcohol consumption in open (428) and double-blind, placebo-controlled trials (1081) with desipramine. Subsequent randomized, double-blind,

controlled trials with desipramine (438) and imipramine (437), as well as a recent meta-analysis (425), concluded that TCAs may offer modest benefits in treating patients with alcohol use disorders and depression but not those with alcohol use disorders in the absence of depression.

Based on animal studies (1082, 1083) and early clinical laboratory findings (1084), the selective serotonin-3 receptor antagonist ondansetron was thought to have effects on alcohol reward and thereby reduce alcohol consumption and promote abstinence. Although patients with early-onset alcoholism and lower levels of drinking showed some benefit with low-dose ondansetron (1085, 1086), other patient subgroups did not demonstrate a response. Replication studies have yet to be conducted, and ondansetron is not approved by the FDA for alcoholism treatment. (Dosing, side effects, and implementation of treatment with ondansetron are discussed in greater detail in Section IX.B.3.d.)

e) Lithium

The use of lithium to treat patients with an alcohol use disorder not comorbid with bipolar disorder was supported by some early anecdotal reports and by a small double-blind, placebo-controlled study (1087). However, a large VA collaborative study (1088) showed no benefits of lithium over placebo for patients with or without depressive symptoms. A more recent meta-analysis also showed no efficacy for lithium in treating alcohol use disorders (1036). Consequently, lithium is not recommended as a primary treatment in patients who do not have co-occurring bipolar disorder.

▶ D. PSYCHOSOCIAL TREATMENTS

A variety of psychosocial treatments have been used in the treatment of alcohol use disorders (1089), and the efficacy of specific psychotherapies for these disorders has been reviewed by a number of authors (79, 956, 1090, 1091). The sections that follow provide an overview of the use of CBT, behavioral therapies, psychodynamic therapies, IPT, self-help groups, brief interventions, marital and family therapy, and aftercare in the treatment of alcohol use disorders.

1. Cognitive-behavioral therapies

CBT and relapse prevention therapies aimed at improving self-control and social skills have been consistently found to reduce drinking (79, 1090, 1092–1094); such cognitive-behavioral therapies, as well as MET and TSF, are therefore recommended for use in individuals with an alcohol use disorder. Cognitive-behavioral stress management interventions and behavioral self-control training (consisting of cognitive and behavioral strategies, including self-monitoring, goal setting, rewards for goal attainment, functional analysis of drinking situations, and the learning of alternative coping skills) produced better outcomes than control treatments in about half of the studies (79, 1090, 1095–1097). Better outcomes during follow-up also seem to occur in individuals who show increased coping responses or "self-efficacy" at the end of treatment (184, 1098–1100) and in those who use problem solving or mastery rather than relying on avoidance of high-risk situations as a coping strategy (43, 265, 959, 1101). In contrast, cognitive therapy interventions that are focused on identifying and modifying maladaptive thoughts but that do not include a behavioral component are not as effective.

In group settings, CBT approaches are similarly effective, although treatment benefits may vary with patient characteristics (1102–1104). Finally, most studies show efficacy for social skills training, which focuses on learning skills for forming and maintaining interpersonal relationships, being assertive, and refusing alcohol (79).

MET and motivational interviewing are typically brief therapies that last one to four sessions and are aimed at maximizing the patient's intrinsic desire to change or enhancing a patient's adherence to more intensive or extended treatment. Motivational approaches have been found to be efficacious in most studies (reviewed by Dunn et al. [1105] and Miller and Wilbourne [79]), including the findings from Project MATCH (43, 90, 265, 1106) in which four

MET sessions given as a stand-alone treatment either initially or as part of posthospitalization care were comparable to 12 sessions of CBT or TSF, with benefits of treatment persisting through 3 years of follow-up.

2. Behavioral therapies

Individual behavioral therapy, particularly involving positive reinforcements for targeted behaviors, has been found to be effective for patients with an alcohol use disorder (191, 956, 1090) and is also a recommended treatment approach. Also effective are behavioral contracting (79) and the community reinforcement approach (190, 1107, 1108), which uses behavioral principles and usually includes conjoint therapy, training in job finding, counseling focused on alcohol-free social and recreational activities, monitoring of disulfiram use, and an alcohol-free social club. When compared with usual outpatient treatment or disulfiram plus a behavioral adherence program, community reinforcement led to significantly better patient outcomes (190, 1108). Community reinforcement also has documented effectiveness in combination with marital therapy (690). Compared with positive reward approaches, aversive therapies have been less successful (79). Relaxation training, although widely studied, has been ineffective in virtually all controlled trials (79).

3. Psychodynamic and interpersonal therapies

There are insufficient studies of adequate research design regarding the use of group or individual psychodynamically oriented psychotherapies for the treatment of individuals with an alcohol use disorder (79, 1090). It is difficult to draw conclusions in this area because of the paucity of well-controlled and designed studies, and the small extant literature is limited by poor research design and short duration of studies. However, there is some clinical consensus that such treatment is particularly helpful when other psychiatric disorders or interpersonal issues are present and when combined with other psychosocial or biological interventions. There are large numbers of patients in this type of treatment, and clinical consensus suggests the therapy is effective in at least some of these patients (956, 1090). In addition to addressing alcohol abuse or dependence, treatment goals often include stabilization of the patient's social and interpersonal life, disorganization of which may both accompany and perpetuate the alcohol use disorder.

4. Brief therapies

Brief interventions are generally delivered over one to three sessions and include an abbreviated assessment of drinking severity and related problems as well as the provision of motivational feedback and advice. Typically studied in general medical or school-based settings and in non-treatment-seeking heavy drinkers, brief therapies have been shown to be effective in reducing alcohol use and improving general health and social functioning (79, 275, 1109). In these subgroups of patients, the efficacy of brief therapies is often comparable with that of longer, more intense treatment; even very brief interventions (i.e., a few hours) may have some positive effect (1110, 1111).

5. Self-help groups and 12-step-oriented treatments

The effectiveness of AA, per se, has not been evaluated in randomized studies. However, other sources of information provide growing support for the utility of AA and 12-step-oriented treatments (259, 261, 956, 958, 959) as well as the efficacy of professional therapies such as TSF that are aimed at motivating patients to participate in AA (43, 219, 265, 267, 269). In addition, a large number of studies have documented that greater AA participation is associated with greater rates of abstinence from alcohol (1112) as well as with better drinking outcomes

(260–266, 289, 1113, 1114). Thus, most patients should be encouraged to attend at least several AA meetings to ascertain the appropriateness and utility of AA in helping them remain alcohol free. Individual patient needs and concerns should, however, be taken into consideration when making this recommendation.

As a spiritual but nonreligious program requiring belief in something beyond oneself (268), AA provides tools for its participants to maintain sobriety, including the 12 steps, group identification, and mutual help. More specifically, "AA is a fellowship of men and women who share their experience, strength and hope with each other that they may solve their common problem and help others to recover from alcoholism. The only requirement for membership is a desire to stop drinking" (253). Al-Anon (friends and family), Alateen (teenage children of alcoholic individuals), and Adult Children of Alcoholics (those who grew up in alcoholic or otherwise dysfunctional homes) help family members and friends of alcoholic individuals focus on the need to avoid enabling behaviors and care for oneself whether a loved one is drinking or not. Other mutual help programs include Women for Sobriety, Rational Recovery, Double Trouble (for patients with alcohol dependence comorbid with other psychiatric disorders), and Mentally Ill Chemical/Substance Abusers.

Patients may be more likely to benefit from AA groups composed of individuals with similar personal characteristics, such as age, sex, or cultural and occupational status. Evidence from small-scale trials on patient-to-program matching suggests that patients with a greater severity of drinking problems, an affective rather than cognitive focus, a concern about purpose and meaning in life, better interpersonal skills, and a high need for affiliation are good candidates for AA (254, 1115). In the landmark Project MATCH study (43), TSF-based aftercare was more effective than that using CBT for outpatients who did not show psychiatric symptoms and was of comparable efficacy for those with psychiatric symptoms. At 1-year follow-up, patients rated as high in seeking meaning of life fared better with TSF compared with MET and CBT, and patients with high social support for abstinence had better drinking outcomes at 1- and 3-year follow-up.

Although official AA policy encourages members to adhere to medical treatment, many individual members interpret the ethos of coping without the use of drugs to mean that recovering individuals should also forgo psychiatric medications (1116). Consequently, patients with a co-occurring psychiatric disorder requiring medication should be encouraged to attend dual-diagnosis AA groups or those in which regular attendees do not oppose medically prescribed psychotropic treatment.

6. Marital and family therapies

For patients who are married or living with family members, such relationships can be an important factor in the posttreatment environment (1090, 1117). Thus, it is not surprising that therapies aimed at enhancing marital or family relationships can be effective in the treatment of alcohol use disorders. In particular, behavioral marital therapy has demonstrated efficacy and cost-effectiveness (79, 225, 236, 238, 690, 961, 1118, 1119). Marital approaches for which there is significant support are Al-Anon facilitation and disulfiram contracting (168, 248); other approaches to marital therapy have shown lesser degrees of efficacy (79).

7. Self-guided therapies

Strong evidence is available to support the efficacy of self-monitoring of drinking patterns, guided by pamphlets provided by practitioners (79). Such approaches have typically been evaluated in general populations of primary care patients or with heavy drinkers who do not meet full criteria for alcohol dependence. Patients presenting to specialized substance use disorder treatment settings have generally experienced multiple failures at self-treatment and are poorer candidates for this approach.

8. Aftercare

A patient's involvement in aftercare after completing inpatient treatment for an alcohol use disorder is an important predictor of outcome (264, 1120, 1121). The lowest rates of relapse have been noted in those completing an aftercare program (1121, 1122), with some evidence that completion rates vary with therapists' efforts to maintain patients in the aftercare program (1122). Although the number of trials on specific aftercare approaches is limited, there is evidence for efficacy for TSF (43, 265), MET (43, 265), CBT administered alone (43, 265) or with coping skills training (223, 1102, 1103), a version of behavioral marital therapy that includes relapse prevention techniques (1118, 1119), insight-oriented interactional group therapy (223, 1102, 1103), and nurse visits delivered over a 12-month period (1123).

▶ E.   CLINICAL FEATURES INFLUENCING TREATMENT

The treatment implications of various clinical features are summarized in Section II.G. In addition to these considerations, specific sequelae and patterns of co-occurring disorders need to be considered for patients with an alcohol use disorder.

1.   Co-occurring psychiatric disorders

Co-occurring psychiatric disorders are common among individuals with an alcohol use disorder. Integrated psychosocial treatments that combine traditional therapies for the psychiatric condition with therapies for the alcohol use disorder have been shown to be effective (376, 1124, 1125). In general, medications recommended to treat patients with an alcohol use disorder alone are also effective in patients with a co-occurring psychiatric disorder, and pharmacological treatment of the psychiatric disorder is similar to that recommended when the psychiatric disorder occurs independently of an alcohol use disorder. Some exceptions to these general principles are discussed below.

Given the propensity of individuals with alcohol and other substance use disorders to misuse prescribed medications, the treating clinician should give preference to prescribing medications that have a low abuse potential. Patients with a high level of depression, impulsivity, or poor judgment or the potential for making a suicide attempt should receive medications with a low potential for lethality in overdose (e.g., SSRIs) (1126, 1127). Given the tendency of patients with co-occurring disorders to have poor medication adherence and an increased risk of overdose, medications should be dispensed in limited amounts, the number of refills should be limited, and random or frequent blood or urine toxicology screening should be used to determine use of both prescribed and nonprescribed medications.

Many patients with alcohol dependence present with signs and symptoms suggestive of major depression or an anxiety disorder. In many patients, however, these signs and symptoms are related to alcohol intoxication or withdrawal and remit in the first few weeks of abstinence (424). Consequently, many psychiatrists feel that patients should be observed over a 3- to 4-week substance-free period before a diagnosis of a co-occurring mood or anxiety disorder is made and a disorder-specific medication is prescribed. Others suggest that in selected cases, earlier initiation of treatment is warranted. For example, depressed patients with particularly severe symptoms, a history of major depression unrelated to periods of alcohol use, and/or a strong family history of mood disorders are more likely to have a co-occurring depression that should be treated soon after detoxification is completed (426–429).

Although studies of SSRIs in individuals with an alcohol use disorder who are not depressed have shown mixed benefit (see Section IV.C.3.d), studies of those who are depressed have shown a moderate positive effect on the patients' addiction and mood (431, 1128, 1129). TCAs may also be effective for alcohol-dependent patients with comorbid depression (425, 437, 438), although the risk of poor adherence, tricyclic-to-alcohol interactions, and overdose should be

considered with such patients. In addition, tricyclic plasma levels may be lower than expected because of the alcohol-induced increase in liver microsomal oxidases (1130, 1131). MAOIs have been used to treat patients with atypical depression, but there is a high risk of poor adherence to dietary and medication restrictions (including those for alcohol) and subsequent adverse reactions (e.g., hypertension) in patients with alcohol use disorders (1132). Consequently, because SSRIs and other nontricyclic, non-MAOI antidepressants have fewer adverse effects and less risk of morbidity and mortality in overdose situations, they are preferred over tricyclic and MAOI antidepressants in the treatment of patients with a co-occurring alcohol use disorder and depression (1133).

Studies of antidepressant agents in individuals with an alcohol use disorder and co-occurring anxiety are limited (1134). Consensus would suggest that these medications can be used as recommended for patients with an anxiety disorder alone.

The use of benzodiazepines for alcohol-dependent patients with comorbid anxiety or panic disorder is more controversial, as benzodiazepines have a high abuse potential in these patients. For patients with generalized or performance anxiety, beta-blockers (e.g., propranolol) and buspirone are preferable to benzodiazepines because they have no cross-tolerance with ethanol or other CNS depressants and minimal abuse potential. Buspirone has also been reported to reduce alcohol consumption in patients with high levels of comorbid anxiety (479, 1135). In patients with otherwise treatment-resistant panic disorder, clonazepam or other long-acting benzodiazepines can be cautiously administered if the principles outlined in Section II.G.2.d.2.d. are observed.

For patients with comorbid bipolar and alcohol use disorders, lithium, valproate, or carbamazepine may be used. A recent double-blind, controlled study of patients with bipolar disorder and alcoholism who were being maintained with valproate showed promising results of this medication as an adjunct to treatment (472). However, when prescribing lithium, valproate, or carbamazepine, the clinician may need to closely monitor the patient for side effects. In particular, the low therapeutic index of lithium may lead to a greater risk of toxicity in individuals with an alcohol use disorder who are actively drinking, and hematological abnormalities may be more pronounced in alcohol-dependent individuals who are treated with valproate or carbamazepine.

In patients with schizophrenia, some data suggest that clozapine may be useful for treating the symptoms of both schizophrenia and a comorbid substance use disorder, including an alcohol use disorder (384, 391, 393, 398), a possibility that requires further study in double-blind, randomized, controlled trials.

2. Comorbid general medical disorders

Chronic high-dose alcohol use can affect several different organ systems, including the gastrointestinal tract, the cardiovascular system, and the central and peripheral nervous systems. Alcohol-induced gastrointestinal problems include gastritis, ulcers of the stomach or duodenum, esophageal varices, portal hypertension, and, in approximately 15% of heavy users, cirrhosis of the liver and pancreatitis (1136–1138). Alcohol-dependent individuals also experience higher-than-average rates of cancer of the esophagus, stomach, and other parts of the gastrointestinal tract (1139, 1140).

Common comorbid cardiovascular conditions include low-grade hypertension and increased levels of triglycerides and low-density lipoprotein cholesterol, which increase the risk of heart disease. Cardiomyopathy occurs primarily among very heavy drinkers (1141).

For men, endocrinological changes associated with chronic alcohol use include decreases in testosterone, loss of facial hair, breast enlargement, decreased libido, and impotence (1142); endocrinological changes for women include amenorrhea, luteal phase dysfunction, anovulation, early menopause, and hyperprolactinemia (1143). Blunting of the thyroid-stimulating hormone response to thyrotropin-releasing hormone, hypoglycemia, ketosis, and hyperuricemia have also been reported (1144, 1145).

Alcohol-induced peripheral myopathy with muscle weakness, atrophy, tenderness, and pain is accompanied by elevations in creatine phosphokinase levels and the presence of myoglobins in the urine (1146). Histological evidence of myopathy can be observed in a significant proportion of patients with an alcohol use disorder, even in the absence of symptoms (1147). When it is severe, alcohol-induced myopathy can involve rapidly progressive muscle wasting.

Many patients seeking treatment of alcohol dependence manifest cognitive abnormalities (1148–1150). Chronic, heavy drinkers can experience an alcoholic dementia with characteristic cognitive deficits that include impairment in short- and long-term memory, abstract thinking, judgment, and other higher cortical functions as well as personality change. Usually the memory deficits are less severe than in Korsakoff's syndrome (alcohol-induced persisting amnestic disorder) or Alzheimer's disease (1151). Neuropathological abnormalities in the frontal lobes, in the area surrounding the third ventricle or diffusely through the cortex, have been reported. More commonly, however, there is subtle cognitive dysfunction that hampers a patient's ability to comprehend or adhere to a treatment plan (1148, 1149, 1152, 1153). For such patients, family members or other responsible parties should be actively involved from the beginning of and throughout the course of treatment. Initial placement of the patient in a more structured (e.g., residential) treatment setting may also be indicated to assess the impact of cognitive problems on the patient's ability to adhere to short- and long-term treatment. In patients who remain abstinent, reversal of alcohol-induced cognitive disturbance is often observed over time (1154, 1155).

Other nervous system sequelae of chronic alcohol use, including peripheral neuropathies, degenerative changes in the cerebellum, Wernicke's encephalopathy, and Korsakoff's syndrome, are related to vitamin deficiencies, particularly deficiencies in thiamine and other B vitamins (1156). Peripheral neuropathy is common, occurring in up to 33% of hospitalized individuals with an alcohol use disorder, with an even greater proportion of alcohol users showing electrophysiological evidence of peripheral nerve damage (1157). Symptoms of alcoholic neuropathy typically include sensory loss, paresthesias, a burning sensation of the feet, numbness, cramps, weakness, calf pain, and ataxia. Ataxia in alcohol-dependent patients can also occur due to cerebellar dysfunction.

Wernicke's encephalopathy is characterized by ophthalmoplegia, ataxia, and confusion (972, 1158). Ocular abnormalities include nystagmus, eye muscle palsies, and pupillary abnormalities. The mortality rate for acute untreated Wernicke's encephalopathy is 15%–20% (1159, 1160); recovery is incomplete in 40% of cases. Most patients (approximately 80%) with Wernicke encephalopathy also develop Korsakoff's syndrome, characterized by anterograde and retrograde amnesia, disorientation, poor recall, and impairment of recent memory coupled with confabulation. Lesions in the mammillary bodies and thalamic nuclei may be the result of vitamin deficiencies or the direct toxic effects of alcohol. Recovery is variable and not possible to predict on the basis of brain imaging. In more than half of the patients, elements of Korsakoff's syndrome are permanent.

These neurological complications should be treated vigorously with B complex vitamins (e.g., thiamine, 50–100 mg/day i.m. or i.v.), usually after adequate fluids and glucose levels are maintained. Some patients may require treatment with B complex vitamins over a prolonged period, and improvements may continue to occur up to 1 year after treatment is begun (1161).

Alcoholic hallucinosis during or after cessation of prolonged alcohol use may respond to antipsychotic medication. Unlike the visual hallucinations that may occur during alcohol withdrawal, these are primarily auditory and occur in conjunction with a clear sensorium (1162).

3. Pregnancy

The general effects of substance use during pregnancy are described in Section II.G.4. Alcohol-related disorders may have specific adverse effects on the health of the pregnant woman, the course of the pregnancy, fetal and early child development, and parenting behavior. The most

well-established effect of in utero alcohol exposure is fetal alcohol spectrum disorder (587, 1163 ,1164). Some children with this disorder will exhibit the characteristic features of fetal alcohol syndrome, including low birth weight, poor coordination, hypotonia, neonatal irritability, retarded growth and development, craniofacial abnormalities (including microcephaly), cardiovascular defects, mild to moderate retardation, childhood hyperactivity, and impaired school performance (586, 972, 1165, 1166). Others will not have the classically described features of fetal alcohol syndrome but will exhibit cognitive and behavioral effects of in utero alcohol exposure (587, 1163, 1164). Thus, the goals in treating pregnant women with an alcohol use disorder include eliminating the use of alcohol, treating any comorbid psychiatric or general medical disorders, guiding the patient safely through the pregnancy, facilitating appropriate parenting behavior, and motivating the patient to remain in treatment after delivery to minimize the risk of relapse.

V. TREATMENT OF MARIJUANA-RELATED DISORDERS

▶ A. OVERVIEW

Marijuana (cannabis) is the most widely used illicit drug in the United States (1167) and in the world. Although marijuana's relative dependence potential is less than that of other substances of abuse, the large number of users will yield high population rates of marijuana dependence (1168). Furthermore, although the overall prevalence of marijuana use has remained stable over the past decade, the initial age at onset of marijuana use has been declining (1169) and the prevalence of marijuana abuse or dependence has increased significantly, perhaps due to an increased potency of available marijuana (1170).

Marijuana use is often considered benign, but it has been associated with a number of psychological, behavioral, and social problems. Marijuana use is common and can be problematic in individuals with other psychiatric disorders, including major mood, anxiety, and personality disorders (1171–1174). Cannabis use can precipitate initial episodes of psychosis in vulnerable individuals (1175) and is associated with an earlier age at first psychotic episode in male patients with schizophrenia, 6.9 years younger than in non-cannabis users (1176). Cannabis abuse or dependence is highly associated with increased risk of other substance dependence (1177).

Contrary to the popular belief among laypeople and professionals that treatment for cannabis dependence is usually neither needed nor sought, the demand for such treatment at substance use disorder programs doubled between 1992 and 1998 in the United States. The percentage of illicit drug abuse treatment admissions for marijuana (23%) approximated that for cocaine (27%) and heroin (23%) (1178). Despite this, the treatment of marijuana abuse and dependence is a comparatively understudied area to date.

▶ B. TREATMENT SETTING

Treatment for marijuana-related disorders usually occurs in an outpatient setting, either individually or in groups. Inpatient treatment is most likely to occur if the individual is hospitalized for another psychiatric disorder, including another substance use disorder.

C. SOMATIC TREATMENTS

Somatic treatments for marijuana dependence have been studied infrequently, perhaps because of the belief held by many that marijuana is a benign substance whose use is easy to stop when desired. However, interest in treatment has grown as evidence from animal and clinical studies has suggested that a withdrawal syndrome occurs if chronic heavy use of cannabis or tetrahydrocannabinol is discontinued (1179–1181). The magnitude and severity of these symptoms appear substantial, and their onset and time course appear similar to those of other substance withdrawal syndromes. Common symptoms are primarily emotional and behavioral, although appetite change, weight loss, and physical discomfort are frequently reported. With our increased knowledge of the marijuana withdrawal syndrome has come a heightened awareness of the drug's role in hampering many individuals from ceasing marijuana use.

Although more attention is now being paid to treatments for marijuana withdrawal symptoms, there have been no successful controlled trials of pharmacotherapy to date. Human trials of medications to ameliorate symptoms of marijuana withdrawal have included bupropion (1182), divalproex (1183, 1184), naltrexone, and nefazodone (1185); all these trials have had negative results. No pharmacotherapy trials to prevent marijuana reinstatement after abstinence have been reported. Thus, no specific pharmacotherapies can be recommended at this time.

D. PSYCHOSOCIAL TREATMENTS

Treatment of cannabis-related disorders has primarily used psychotherapies (1178). Specific psychosocial approaches that have been studied in the treatment of marijuana dependence have included a brief motivational approach and a more intensive relapse prevention approach that combines motivational approaches with coping skills development. Compared with delayed treatment control conditions, both treatments decreased marijuana use (276, 1186–1188), and, in the more robust study, intensive treatment showed a greater impact through the 15-month follow-up period (276). Adding voucher-based incentives to coping skills and motivational enhancement may lead to further improvements in outcomes (201). Nonetheless, even after achieving at least 2 weeks of abstinence, rates of relapse among marijuana-dependent patients receiving behavioral/psychosocial treatment are high, reaching >67% by 6 months in one study (1189). A recent study of a manual-guided, group-based treatment for adolescents with mild to moderate substance abuse found that marijuana use (but not alcohol use) was significantly reduced at 6 months, with the reduction sustained at 12 months (1190). Thus, although there are few studies of psychosocial treatments for marijuana dependence, those that have been conducted show evidence of benefit, particularly with more intensive approaches. Given the lack of pharmacotherapies for marijuana dependence and its psychological, behavioral, and social consequences, psychosocial treatments such as motivational therapy and relapse prevention are recommended for those with marijuana dependence.

E. PREGNANCY

There is increasingly robust evidence that marijuana use during pregnancy is associated with a number of deleterious outcomes. Case-control data (1190a) obtained at 17–22 weeks of gestation suggest that marijuana exposure has negative effects on fetal growth as measured by foot length and body weight. Behavioral, cognitive, and academic difficulties have also been observed in longitudinal follow-up studies of individuals with prenatal exposure to marijuana. As with prenatal exposure to maternal smoking or alcohol use, maternal use of marijuana during pregnancy appears to be related to increased impulsivity (1190b, 1190c), inattention (1190c, 1190d), and externalizing behaviors during childhood (1190c). Learning and memory tasks

(1190b, 1190c) and other aspects of cognitive functioning, such as executive functioning or visual analysis and hypothesis testing (1190d), also seem to be negatively affected by prenatal marijuana exposure.

Data from the 10-year follow-up of mother-child pairs who participated in the Maternal Health Practices and Child Development Project indicated differences in the effects of maternal marijuana use depending on the trimester in which exposure occurred. For example, independent of prenatal alcohol exposure, first-trimester marijuana exposure was associated with deficits in reading and spelling scores and lower teacher ratings of performance, whereas second-trimester exposure was associated with impaired reading comprehension and school performance (1190e). In the same cohort, prenatal marijuana exposure in the first and third trimesters predicted significantly increased levels of depressive symptoms in offspring at 10-year follow-up (1190f). An additional longitudinal study found that prenatal exposure to marijuana was associated with increased likelihood of both cigarette smoking and marijuana use in 16- to 21-year-old adolescent offspring compared with adolescents whose mothers had not used marijuana during pregnancy (1190g).

These findings suggest that pregnant women should be asked about marijuana use and advised to abstain from marijuana use during pregnancy.

VI. TREATMENT OF COCAINE-RELATED DISORDERS

▶ A. OVERVIEW

At the time of the 2003 National Survey on Drug Use and Health (1191), approximately 2.3 million individuals were currently using cocaine, with approximately 33% of that group smoking crack cocaine. In addition, 1.1 million people used cocaine for the first time during that year. Although this figure does not approach the peak of 1.6 million new users seen in 1980, it does represent a slight increase over the approximately 1 million new users in each of the previous 3 years.

In recent years, the abuse of methamphetamine has also become a significant public health problem, beginning primarily in Hawaii, the West Coast, and the southwestern United States and steadily moving eastward.

Although this section focuses on cocaine dependence, pharmacotherapy of amphetamine dependence is expected to be similar. Neither disorder has an FDA-approved pharmacotherapy, and very few clinical trials have been completed with amphetamine-dependent patients, with none of these studies showing different results than those described later for cocaine dependence (1192, 1193). A possibly significant difference between cocaine and amphetamine is cocaine's interaction with alcohol to form cocaethylene. This metabolite has cocaine-like effects and toxicity (1194–1196).

▶ B. TREATMENT SETTINGS

Patients with a cocaine or other stimulant use disorder generally do not require treatment in an inpatient setting as withdrawal syndromes are not severe or medically complex. Several studies have indicated that most patients can be effectively treated for cocaine abuse in intensive outpatient programs (1197, 1198).

► C. SOMATIC TREATMENTS

1. Treating intoxication

The treatment of acute cocaine intoxication has been the subject of relatively little systematic investigation. In general, because there is no specific antidote to cocaine, treatment is typically supportive and aimed at treating symptoms such as delusions or autonomic hyperactivity. Cocaine intoxication can produce hypertension, tachycardia, cardiac arrhythmias, coronary artery vasospasm, myocardial infarction, stroke, and seizures (1199). Although the beta-blocker labetalol has been cited as being helpful in reducing this cocaine toxicity, animal studies and some clinical experience suggest that the use of adrenergic blockers and dopaminergic antagonists should be carefully monitored when treating acute cocaine intoxication (1200–1202). Benzodiazepines are used for acute cocaine intoxication in patients who become extremely agitated and/or potentially dangerous (1203). Although antipsychotic medications have been reported to be effective in treating delusions associated with cocaine intoxication, most individuals recover spontaneously within hours (1204, 1205) and thus require no treatment (1206–1208). There is no evidence that anticonvulsants prevent stimulant-induced seizures, and they are not recommended for this purpose.

2. Treating withdrawal

The clinical features and duration of the cocaine abstinence syndrome are still somewhat controversial. Although anhedonia and cocaine craving are common (1204), craving can be difficult to define (1204, 1209), and the cessation of cocaine use does not always cause specific withdrawal symptoms. However, many people do experience a characteristic withdrawal syndrome within a few hours to several days after the acute cessation of, or reduction in, heavy and prolonged cocaine use. An early uncontrolled outpatient study (1204) characterized withdrawal as progressing from a "crash" associated with intense depression, fatigue, and at times suicidal ideation to dysphoria and sleep difficulties lasting 1–10 weeks. Results from more recent inpatient studies (1209, 1210) and one outpatient study (1211) have suggested that cessation of regular cocaine use is associated with relatively mild symptoms of depression, anxiety, anhedonia, sleep disturbance (insomnia or hypersomnia), increased appetite, and psychomotor retardation, which decrease steadily over several weeks.

Dopamine agonists, such as amantadine (200–400 mg/day), were initially thought to be effective in reducing symptoms of cocaine withdrawal, craving, and subsequent use (1212–1214), but two other studies (1209, 1215) failed to confirm this finding. Similarly, initial studies of bromocriptine yielded promising results in the treatment of cocaine withdrawal (1216, 1217). A subsequent randomized, double-blind, controlled trial (1214) found a higher rate of cocaine-negative urine samples but a higher dropout rate among patients given bromocriptine than among patients given amantadine. An uncontrolled inpatient study (1218) found no reduction of cocaine craving with bromocriptine, and a randomized, double-blind, controlled trial (1219) found no significant difference between bromocriptine and placebo in reducing cocaine use in outpatients. Finally, a large study of pergolide (1220) found no difference from placebo in either symptom reduction or continued cocaine use.

Propranolol has recently been shown to have promise in reducing cocaine withdrawal symptoms, although its efficacy as a pharmacotherapy for cocaine dependence in general appears to be limited to those with relatively severe withdrawal symptoms (1221). There may be a subgroup of patients who will respond to some form of pharmacotherapy with reduced craving and, subsequently, reduced use (see below); however, to date there are few research data to help the psychiatrist identify such patients.

3. Medications to treat cocaine dependence

For many patients, pharmacological treatment is not ordinarily indicated as an initial treatment of cocaine dependence because no medication has been found to have clear-cut efficacy (1222–1225). However, a number of studies have shown promising results with pharmacotherapeutic agents, and patients with more severe forms of cocaine dependence (e.g., those with more severe cocaine withdrawal symptoms) (1221, 1226) or patients who do not respond to psychosocial treatment may be candidates for a pharmacotherapy trial.

Studies of desipramine have yielded inconsistent findings, with some studies showing benefit of the medication (1227–1229) and others showing no response by patients (1215, 1230, 1231). An additional study that compared desipramine with placebo showed improvement with desipramine in the short term (6 weeks) but not at 12 weeks or 1 year (503). Interpretation of studies of desipramine may be confounded by differences in patient population, route of cocaine administration, and use of concomitant psychotherapies or other pharmacotherapies. Fluoxetine (1232, 1233) and bupropion (1234) have also shown some benefit in small studies but have demonstrated no superiority to placebo when evaluated in larger trials (413, 1235–1238).

The evidence for using dopamine agonists in treating cocaine dependence is also mixed. Of the dopamine agonist medications, amantadine is the best studied but has shown no overall benefit in most studies (1225, 1231, 1239). However, it may be useful for some patients, as it did demonstrate efficacy in one controlled trial (1240) and in another trial may have led subjects with more severe withdrawal symptoms to have a better response (1226). Inconclusive or negative findings have been seen with other dopamine agonists, including selegiline (1241; F. Vocci, personal communication), L-dopa/carbidopa (1242), and pergolide (1220, 1243). Although replacement therapies with methylphenidate or sustained-release amphetamine are associated with better patient retention and greater reduction in cocaine use than placebo, these studies need further replication (1244–1247).

In treating patients who are dually dependent on cocaine and opioids, the mixed opioid agonist-antagonist buprenorphine has shown some promise in open trials (1248, 1249) but not in large-scale double-blind studies (1250–1252). Again, responses may vary depending on factors such as buprenorphine dose, with doses of 12–16 mg/day being more effective (1253), or concomitant treatment (e.g., desipramine plus contingency management) (1228, 1229, 1254). Naltrexone has also been tested but has not been found to be useful for cocaine dependence (1255).

Although initial studies of the anticonvulsant carbamazepine showed some favorable results in the treatment of cocaine dependence (1256), subsequent double-blind, placebo-controlled studies failed to confirm this (1257–1261). More recent research, including one double-blind study (1262), has suggested some promise for another anticonvulsant, topiramate, for cocaine-dependent patients. The GABA$_B$ agonist baclofen has shown some success in treating cocaine dependence (1263), and a recent double-blind clinical trial of tiagabine, a GABA reuptake blocker, was superior to placebo for reducing cocaine use (1264). However, these findings require replication. Modafinil (400 mg/day) has recently shown some efficacy for reducing cocaine abuse in an 8-week controlled study and merits further investigation (1265). Two previous cocaine interaction studies also support the potential efficacy and safety of modafinil (1266, 1267).

4. Medications to change the subjective effects of cocaine

Attempts to find a medication that blocks or attenuates the subjective (e.g., euphorigenic) effects of cocaine have included trials of neuroleptics (1268, 1269) and mazindol (1270–1273), neither of which has been shown to be effective. Recent data with disulfiram suggest that this medication may increase the aversive effects of cocaine and reduce its use (1274–1277). Other

recent work has suggested that a cocaine vaccine may induce the formation of sufficient antibodies to reduce cocaine use (1278).

5. Acupuncture

Acupuncture is a somatic treatment that has been frequently used in the treatment of patients with a substance use disorder. Two recent large randomized, controlled trials (1279, 1280) of auricular acupuncture, a type of acupuncture that is supposed to be helpful specifically for patients with a substance use disorder, found the treatment to be no more effective than relaxation techniques or the needle insertion/sham acupuncture control condition. Moreover, cocaine craving and physiological arousal were not differentially affected by auricular acupuncture compared with sham acupuncture (1281). Although many studies have reported positive results for the use of acupuncture in clinical settings (1279, 1282–1287), none have used randomized assignment or appropriate controls. Thus, evidence for the benefits of acupuncture is weak, and if acupuncture is used, it should be part of a biopsychosocial treatment approach.

▶ D. PSYCHOSOCIAL TREATMENTS

1. Cognitive-behavioral therapies

For the treatment of cocaine dependence, CBT confers greater therapeutic benefits than less-intensive approaches that have been evaluated as control conditions (267, 1288). It is at least as effective as manual-guided disease-model approaches (267, 1289) and can be associated with further decreases in cocaine use even after subjects leave treatment (1192, 1275, 1290, 1291). Furthermore, CBT appears to be particularly effective with more severe cocaine users or those with a comorbid disorder (229, 452, 503, 1289, 1292, 1293).

2. Behavioral therapies

The effectiveness of contingency management as a treatment for cocaine dependence has been demonstrated by Higgins and colleagues (188, 191–194, 1294). In addition to their work, the benefits of contingency management procedures have been replicated in other settings and samples, including cocaine-dependent individuals receiving methadone maintenance (195, 196, 1295, 1296), substance-abusing homeless individuals (1297), freebase cocaine users (1298), and pregnant substance users (1299).

3. Psychodynamic and interpersonal therapies

No randomized clinical trials have been conducted for psychodynamically oriented treatments for cocaine abuse or dependence, although a case series of individual psychodynamically oriented psychotherapy (1300) and reports of psychodynamically oriented group psychotherapy (1301, 1302) have supported the efficacy of this approach. The clinical study of IPT has been limited to a single 12-week randomized trial in cocaine-dependent outpatients in whom CBT was found to be superior to IPT (1276). Supportive-expressive therapy has been studied as part of the NIDA Collaborative Cocaine Treatment Study, a multisite randomized trial of psychotherapeutic treatments for cocaine dependence, and was found to be less effective than individual plus group drug counseling in decreasing cocaine use (219).

4. Self-help groups and 12-step-oriented treatments

Although self-help groups have not been shown to be a sufficient alternative to professional treatment (1303), greater participation in AA, Cocaine Anonymous, or other 12-step self-help groups seems to predict less cocaine use at subsequent follow-up points (256, 1304).

Manual-guided, professionally delivered treatments are based on 12-step principles, and patients treated with these approaches are actively encouraged (but not required) to attend AA or Cocaine Anonymous meetings, become involved in traditional fellowship activities, and maintain journals of their self-help group attendance and participation. These therapies, including TSF (268) and individual drug counseling (219, 269, 1305), also have demonstrated efficacy in treatment of cocaine use disorders. For example, in alcoholic cocaine-dependent individuals, TSF was found to be significantly more effective than clinical management, was comparable with CBT in reducing cocaine use (267), and was associated with continuing reductions in cocaine use throughout the follow-up period. Furthermore, the attainment of significant periods of abstinence during treatment was associated with abstinence during follow-up, emphasizing that the inception of abstinence is an important goal of treatment (194, 1275).

The effectiveness of 12-step-oriented individual drug counseling (269) was demonstrated in the NIDA Collaborative Cocaine Treatment Study (219, 1305). Cocaine use was significantly reduced relative to baseline use after intensive treatment (36 individual and 24 group sessions over 24 weeks, for a total of 60 sessions) with group drug counseling alone; cognitive therapy (1306) plus group drug counseling; or supportive-expressive therapy, a psychodynamically oriented approach (217), plus group drug counseling. However, the greatest reductions in cocaine use were noted with 12-step-based individual drug counseling plus group drug counseling (219); 12-step-oriented standard group counseling also appears to be comparable in efficacy with relapse prevention aftercare (229).

▶ ## E. CLINICAL FEATURES INFLUENCING TREATMENT

The treatment implications of various clinical features are summarized in Section II.G. In addition to these considerations, specific sequelae and patterns of co-occurring disorders need to be considered for patients with a cocaine use disorder.

1. Specific co-occurring psychiatric disorders

Co-occurring psychiatric and medical disorders are common among cocaine-dependent patients (1307). Several reports have addressed the treatment of patients with a psychiatric disorder who also have a cocaine-related disorder (1308–1315). Specific treatments that have been reported to be effective in certain populations of patients with cocaine abuse include lithium for patients with co-occurring bipolar disorder, desipramine for patients with co-occurring depression, and bromocriptine for patients with co-occurring ADHD (1223, 1310, 1311, 1316). In addition, the results of a randomized, double-blind, placebo-controlled trial (445) suggest that desipramine or amantadine treatment for depressed cocaine-abusing, methadone-maintained patients may reduce cocaine use. Several focused and reasonably well-controlled studies have shown that patients with schizophrenia who primarily abuse cocaine experience some decreases in craving with antipsychotic agents (401, 1317–1319). Given the evidence to date, however, these treatments alone cannot be expected to reduce cocaine use in these patients and must therefore be accompanied by appropriate psychosocial treatment for a cocaine use disorder (1309, 1310).

2. Comorbid general medical disorders

A range of general medical conditions are associated with cocaine use, depending on the route of administration of cocaine. Intranasal use may cause sinusitis, irritation and bleeding of the nasal mucosa, and nasal septum perforation. Smoking cocaine is associated with respiratory problems, such as coughing, bronchitis, bronchospasm, and pneumonitis, resulting from irritation and inflammation of the tissues lining the respiratory tract (1320, 1321). Barotrauma such as pneumothorax, pneumomediastinum, and pneumopericardium may occur as a result of coughing or a Valsalva-like maneuver that is performed to better absorb the drug (1322, 1323).

Puncture marks and "tracks," most commonly in the forearms, occur in individuals who inject cocaine. HIV infection is associated with cocaine dependence as a result of frequent injections, increased promiscuous sexual behavior, or both; other sexually transmitted diseases, hepatitis, tuberculosis, and other lung infections are also seen, as described in DSM-IV-TR (p. 247).

General medical conditions independent of the administration route of cocaine include weight loss and malnutrition from appetite suppression, myocardial infarction, and stroke (657, 1225, 1324). Seizures, palpitations, and arrhythmias have also been observed in cocaine-using individuals. Among individuals who sell cocaine, traumatic injuries from violent behavior are common, as described in DSM-IV-TR (p. 248).

3. Pregnancy

In addition to the general effects of substance use during pregnancy (Section II.G.4), cocaine-related disorders may have specific adverse effects on the health of the pregnant woman, the course of the pregnancy, fetal and early childhood development, and parenting behavior. Possible effects of cocaine use on the course of the pregnancy include irregularities in placental blood flow, abruptio placentae, and premature labor and delivery, as described in DSM-IV-TR (p. 248). Although earlier studies suggested that cocaine use during pregnancy results in adverse effects on fetal development (e.g., very low birth weight, congenital anomalies, urogenital system malformations, mild neurodysfunction, transient electroencephalographic abnormalities, cerebral infarction, seizures, vascular disruption syndrome, smaller head circumference) (1325–1328), more recent studies (583, 1329) have challenged the specific role of cocaine in adversely affecting the course of pregnancy. Behnke et al. (1329) assessed the offspring of a sample of 154 identified cocaine users and a matched group of 154 non-cocaine-using control subjects to compare perinatal outcomes. The cocaine-exposed infants were significantly more likely to be premature and have smaller birth weight, length, and head circumference but showed no other major or minor anomalies to a greater degree than non-cocaine-exposed infants. Addis et al. (583) conducted a meta-analysis of 33 studies of the potential teratogenicity of cocaine. They found that although all of the complications they examined (prematurity, abruptio placentae, low birth weight, prevalence of major malformations, premature rupture of membrane, and mean birth weight, head circumference, and length) demonstrated worse outcomes in infants who had been exposed to cocaine in utero than those who had not, only the risk for abruptio placentae and premature rupture of membrane remained statistically associated with cocaine use. Thus, although children of women who used cocaine during pregnancy did appear to have worse perinatal outcomes, this may have been due to other factors associated with cocaine or other substance use during pregnancy.

The possible effects on early childhood development that have been reported in cocaine-exposed newborns include hypertonicity, spasticity, convulsions, hyperreflexia, irritability, and inattention. However, the role of exposure to cocaine or other substances, poor maternal nutrition, birth prematurity, low infant birth weight, and neonatal withdrawal in the development of these signs and symptoms remains unclear (1330, 1331). Signs of CNS irritability usually disappear within the first year of life, as do any differences in head circumference or retardation in brain growth. Studies in cocaine-exposed children have revealed deficits in attention span at 7 months, and in utero exposure to amphetamines has been found to be associated with slightly lower IQs (albeit still in the normal range) in 4-year-old children (1332). A recent review of early child development after prenatal cocaine exposure (1333) systematically examined 36 studies on this subject and documented no independent effects of cocaine exposure on most measures of child development, although it did find that some reduction in attentiveness and emotional expressivity may occur. Thus, although no clear correlation between in utero cocaine exposure and subsequent intellectual or neurological development has been established, associated conditions, such as low birth weight, the complications of untreated (or

undertreated) withdrawal, and congenital abnormalities may have adverse effects on offspring's cognitive and psychosocial development. In addition, as stated above, many children of women who used cocaine during pregnancy have other risk factors that may affect their development.

A clinician who is developing a treatment plan for a pregnant patient who is withdrawing from cocaine should take into account the risks and benefits to the mother and fetus in deciding about the use and choice of pharmacotherapies. When present, the concurrent use of other substances will also need to be addressed.

VII. TREATMENT OF OPIOID-RELATED DISORDERS

▶ A. OVERVIEW

According to the 2003 National Survey on Drug Use and Health (1191), there were approximately 3.7 million lifetime users of heroin in 2003. Of these lifetime users, 314,000 individuals had used heroin in the previous year and 169,000 reported heroin dependence at some point in the previous year. This suggests that a high proportion (54%) of individuals who used heroin in the previous year were dependent on this opiate. These numbers are likely to be significant underestimates because of the difficulty in ascertaining community rates of heroin dependence; the Office of National Drug Control Policy estimates that 750,000 to 1,000,000 individuals are heroin dependent (1333a).

Heroin is not the only opiate that is abused; there has been a growing awareness of misuse or "nonmedical use" of prescription pain relievers (e.g., hydromorphone, morphine, oxycodone, codeine, propoxyphene). The 2003 survey found that there were approximately 31.2 million individuals who reported nonmedical use of prescription pain relievers in their lifetime, a rate markedly higher than the rate of lifetime heroin use. Approximately 11.7 million reported using opiates for nonmedical reasons in the previous year, and 943,000 individuals fulfilled criteria for opioid dependence that same year. Although a considerably lower proportion of individuals with past-year use were dependent on prescription opioid pain relievers compared with heroin (8% vs. 54%), it is important to note that over five times as many individuals are dependent on prescription opioid pain relievers than on heroin.

Given the number of individuals who are using and are dependent on opiates, it is not surprising that the most commonly studied substance-related conditions, and those for which treatments have been most extensively studied, are opioid dependence, opioid abuse, opioid intoxication, and opioid withdrawal. Treatment for opioid-related conditions can be highly effective. Interventions include pharmacological treatments with agents such as methadone, buprenorphine, and naltrexone and nonpharmacological services such as behavioral therapies and counseling. The treatment of opioid dependence, in particular, is one of the most extensively researched areas in the field of addictions, and the range of available treatments is more extensive than for most other substance use disorders.

Despite the number of effective treatments for opioid dependence and the scientific basis for their efficacy and safety, the availability of treatment programs for this and other illicit drug use is limited. Among the multiple factors that probably contribute to the limited availability of such treatment generally and opioid dependence treatment in particular are the social stigma associated with treatment facilities and their patient population, limited funding for treatment, and a history of variability in the quality of treatment supplied by clinicians and existing programs. In addition, social ambivalence about the nature of addictions and the medicalization

of substance use disorder treatment may be significant contributing factors for the difficulty of expanding such treatment.

There are two general thoughts regarding the treatment goals for patients with an opioid use disorder: 1) there should be abstinence from all illicit opioid use or 2) there should be a substantial decrease in use but abstinence is not an absolute requirement. The logic of the latter is that decreased use of illicit substances will translate into lower rates of risky behavior and that this is a worthy goal of treatment. Although these two general goals may seem opposed, it may be helpful to conceptualize the latter as an acceptable intermediate stage toward the ultimate achievement of the first goal—abstinence.

Additional goals of treatment include addressing other substance use, psychosocial outcomes (e.g., impact of drug use on employment, reconciliation with family members), and psychiatric and somatic needs (e.g., treatment for comorbid affective disorders, management of chronic physical disorders). Treatment goals will vary depending on the circumstances of the particular patient, the specific opioid-related disorder for which the patient seeks treatment, the treatment setting, the resources available to the practitioner, and the resources available to the patient.

Defining specific goals that are applicable to all patients is unrealistic, but a few further general points regarding treatment goals are worth noting. For example, cessation or stabilization of substance use should be an early and primary treatment goal. It is probably premature to attempt to rectify many early psychiatric symptoms or psychosocial problems while a patient is actively using opioids. However, exceptions may be made in certain circumstances, such as with a patient who has a clear history of a psychiatric disorder that is independent of the substance use or a patient who is acutely suicidal. In particular, the patient who maintains that he or she needs pharmacological treatment for anxiety or depressive symptoms to control illicit opioid use is probably best initially managed with a focus on the substance use. Another general treatment goal may include educating patients about the possibility of relapses during treatment and the importance of making a plan to prevent further substance use if a relapse occurs. Finally, treatment expectations, such as the patient's behavior (e.g., tardiness, missed appointments, presenting while intoxicated) and the clinician's responsibilities (e.g., providing emergency contact information, providing other resources to optimize outcomes) are related to treatment goals and may be addressed through a discussion with the patient.

▶ B. TREATMENT SETTINGS

In general, there are five settings or modalities in which most treatment of opioid-related disorders occurs: inpatient hospital settings, outpatient clinics and offices, opioid treatment programs, self-help programs, and therapeutic communities. The choice of treatment setting depends on the clinical characteristics and preferences of the patient, the patient's perceived treatment needs, and the available alternatives. As in the treatment of all patients, the least restrictive setting that is likely to facilitate safe and effective treatment is preferred.

There are some general guidelines and recommendations for treatment settings for opioid-related disorders. An opioid overdose, which in severe cases can be a life-threatening emergency, should be evaluated and initially managed in a supervised medical setting such as an emergency department or inpatient service. Treatment typically includes reversal of opioid effects with an opioid antagonist (e.g., naloxone). Opioid withdrawal may also be treated in an inpatient setting and can be effectively managed with pharmacological agents such as opioid agonist medications (e.g., methadone, buprenorphine) or nonopioid medications (e.g., clonidine). Although management of opioid withdrawal symptoms can be effectively achieved relatively quickly in an inpatient setting (i.e, within 7 days), long-term outcome for such withdrawal is generally poor, with high rates of relapse after discharge from the controlled setting. Continued

treatment for the opioid use disorder after withdrawal is indicated in most cases. Inpatient opioid withdrawal without specific outpatient follow-up (e.g., drug-free treatment) is an inadequate intervention that has a low likelihood of long-term success.

The second possible setting is outpatient clinics and offices. This can include so-called drug-free programs (treatment programs that do not provide opioid agonist medications to the patient), group practices, and the individual practitioner's office. Drug-free programs can provide services to patients who have undergone an inpatient, medically supervised opioid withdrawal. Although these programs do not provide opioid agonists to patients, they may provide naltrexone for the treatment of opioid dependence. Group practices and the individual practitioner's office may provide buprenorphine or naltrexone for the treatment of opioid dependence. The Drug Addiction Treatment Act of 2000 allows physicians in the United States to prescribe schedule III, IV, and V medications that are approved for the treatment of opioid dependence from office-based settings, although there are stipulations on this practice. Currently, sublingual buprenorphine and sublingual buprenorphine plus naloxone are the only FDA-approved agents for this purpose. There also has been interest in developing office-based methadone treatment, which is generally not available in the United States except under certain circumstances in which a physician works with an opioid treatment program (1334).

Outpatient opioid treatment programs, a third treatment setting, are primarily methadone maintenance programs, although buprenorphine can also be provided in this setting. These operate under special federal and state regulations, and expansion of this modality has been difficult in many parts of the United States. However, when properly operated, these programs can be highly effective for patients who have been unable to maintain abstinence from illicit opioid use. Methadone maintenance is the most common form of pharmacological treatment for opioid dependence, with more than 240,000 individuals estimated to be receiving methadone treatment in the United States in 2004. Routine office-based pharmacological treatment with buprenorphine, and possibly methadone, in the future has considerable promise based on research studies and the growing clinical experience with this form of treatment in the United States. Experience from France (1334a) suggests these treatments can substantially reduce opioid-related mortality, but there is a risk of buprenorphine diversion to other uses and abuse in the outpatient setting.

Self-help programs such as Narcotics Anonymous are another form of treatment used by individuals with opioid abuse or dependence. Because anonymity is an integral part of these programs, it is difficult to know the extent of their utilization, outcomes achieved, or factors that predict a particular person's success in such programs. However, anecdotal reports from patients and the pervasive availability of the meetings suggest these programs serve a valuable function and are effective for many people who have used illicit opioids. Self-help groups can also be effective when used within the different treatment settings previously discussed (see Section II.F.8).

Therapeutic communities are yet another treatment setting for patients who abuse or are dependent on opiates (see Section II.C.2.d). Therapeutic communities can be an effective treatment for some patients with opioid dependence but have decreased in prominence over time. However, there is renewed interest and evidence of efficacy for therapeutic communities in special circumstances, such as with criminal justice populations.

▶ C. SOMATIC TREATMENTS

1. Treating dependence and abuse

a) Full mu agonist therapy: methadone and LAAM

There are two approved full mu agonist opioid medications available for the treatment of patients with chronic and relapsing opioid dependence: methadone and LAAM, both schedule II

medications. Methadone is the most thoroughly studied and widely used pharmacological treatment for opioid dependence (1335, 1336). It is orally active, can be dosed once per day, and at sufficient doses does suppress opioid withdrawal and block the effects of other opioids. LAAM is structurally related to methadone and shares many similar features (oral activity, withdrawal suppression, blockade effects) but has a longer duration of action, allowing dosing on a less than daily basis. Although it is still an FDA-approved medication, LAAM has been withdrawn from the United States market by its manufacturer because of an associated risk of cardiac arrhythmias (1337).

Each of these medications is available only through specially licensed opioid treatment programs. Oversight of these programs was recently shifted from the FDA to SAMHSA, and the programs are now accredited by an outside agency such as the Joint Commission on Accreditation of Healthcare Organizations. Many of the prior treatment regulations have been revised (including greater flexibility in take-home doses of medication).

The primary goals of opioid agonist maintenance treatment are to 1) achieve a stable maintenance dose that suppresses withdrawal, reduces opioid craving, blocks the effects of illicit opioids, and eventually stops illicit opioid use; and 2) facilitate patient engagement in a comprehensive program designed to prevent dependence or abuse of other substances and promote rehabilitation.

The choice of treatment for opioid dependence is based on patient preference, assessment of the patient's past response to treatment, the probability of the patient's achieving and maintaining abstinence for the different treatment modalities, and the physician's assessment of the short- and long-term effects of continued use of illicit opioids on the patient's life adjustment and overall health status. Because methadone maintenance may become a lifelong therapy, some physicians prefer to avoid it as a first-line treatment for opioid dependence in adolescents. In addition, the higher demand versus availability of opioid treatment programs can be an additional and significant factor influencing referral to this type of program.

Methadone maintenance treatment for opioid-dependent individuals has generally been shown to be effective in 1) decreasing illicit opioid use, 2) decreasing psychosocial and general medical morbidity associated with opioid dependence, 3) improving overall health status, 4) decreasing mortality, 5) decreasing criminal activity, and 6) improving social functioning (171, 1338–1340). Several studies also support the usefulness of methadone maintenance in reducing the spread of HIV infection among intravenous drug users (1341). It should be noted that methadone maintenance treatment involves a combination of methadone medication and nonpharmacological services. The latter can include individual and group counseling, urine testing, and behavioral treatments, with the purpose of addressing opioid and other substance use as well as the psychosocial problems associated with drug use. Further discussion of psychosocial treatments for opioid-related disorders is provided in Section VII.D.

One of the key issues in methadone maintenance is determining a dose sufficient to suppress the patient's opioid withdrawal and craving, as no single dose is optimal for all patients. Some may benefit from maintenance on lower doses such as ≤40 mg/day, whereas others may require >100 mg/day to achieve maximum benefit. Controlled studies of methadone dosing have not tested daily doses of >100 mg/day, although there are anecdotal reports of such use in the United States, and doses greater than 100 mg/day are used in several other countries (1342–1346). Although 40–60 mg/day of methadone (and sometimes less) is usually sufficient to block opioid withdrawal symptoms (1339), higher doses are usually needed during maintenance treatment to block craving for opiates and associated drug use. Higher doses of methadone are also generally needed for heroin addicts with axis I psychiatric comorbidity (1347, 1348). In general, higher doses are associated with better treatment retention and lower rates of illicit opioid use (1349–1352).

Maintenance on methadone is generally safe. Methadone undergoes hepatic metabolism by CYP 450 3A4 in conjunction with other P450 enzymes; its half-life is approximately 24 hours,

so methadone can be administered once daily (1353). However, other concurrent medications and/or substances of abuse that a patient might be taking need to be considered because they may induce symptoms of withdrawal, toxicity, and even death by interfering with the metabolism of methadone (1354, 1355). The most common side effects of methadone are constipation, increased sweating, and sexual difficulties. Although early studies of methadone found the medication had no significant effect on cognition or performance measures (1356–1358), other studies have found evidence of some subtle but significant effects (1359, 1360). Finally, overdose with methadone or any mu agonist can produce respiratory depression and death. Methadone can be used as an analgesic, and there has been evidence of increased methadone-related deaths as the frequency of prescribing methadone for pain management has increased. Methadone can be diverted for abuse, as can other opiates that have agonist effects at the mu receptor (e.g., LAAM, buprenorphine).

b) Partial mu agonist therapy: buprenorphine

Buprenorphine is a mixed opioid agonist-antagonist with a pharmacological profile different from that of full mu agonists such as methadone. Buprenorphine produces a less than maximal or partial agonist effect at the mu receptor (its primary action with respect to the treatment of opioid dependence) and an antagonistic effect at the kappa receptor (126). These receptor interactions are thought to account for buprenorphine's unique profile of effects, which have clinical implications for treating opioid dependence.

Buprenorphine has been marketed worldwide as a parenteral analgesic for many years. Because it has poor oral but fair sublingual bioavailability, a sublingual buprenorphine tablet has been developed for the treatment of opioid dependence. Buprenorphine enters the bloodstream more slowly through the sublingual route than with parenteral administration and thus has less abuse potential compared with the parenterally delivered form. There are two forms of the sublingual tablet: a buprenorphine-only tablet and a combination tablet of buprenorphine and the opioid antagonist naloxone. Because naloxone has poor sublingual but good parenteral bioavailability (1361), it is hoped that the combination tablet may decrease the risk of buprenorphine diversion to other uses and parenteral abuse even further because naloxone used parenterally will precipitate opioid withdrawal in opioid-dependent patients. Both forms of buprenorphine tablets are schedule III medications in the United States.

Like methadone, buprenorphine can suppress opioid withdrawal and block the effects of other opioids. Clinical trials comparing daily sublingual buprenorphine (equivalent of 12–16 mg of the tablet form per day) to moderate doses of daily oral methadone (i.e., 50–60 mg/day) have generally shown comparable outcomes on treatment retention and decreased illicit opioid use (1251). However, higher doses of methadone (≥80 mg/day) appear to produce superior outcomes to daily buprenorphine (1250, 1251, 1336, 1362–1364). It is not known if comparable effects could be produced by increasing the dose of buprenorphine; current evidence suggests buprenorphine may be best suited for patients with mild to moderate levels of physical dependence. Nonpharmacological treatment in combination with buprenorphine can help to achieve abstinence. For example, a study by Galanter et al. (1365) demonstrated that psychosocial support (in this study, network therapy) tailored to promoting abstinence from illicit opioids during buprenorphine maintenance can improve clinical outcomes.

Buprenorphine has a long duration of action and can be dosed on a less than daily basis. When used in this way, the dose administered should be increased to compensate for the longer between-dose interval (for example, doubling the daily dose for a 48-hour interval and tripling the daily dose for a 72-hour interval). Between-dose intervals of 48–72 hours are generally well tolerated in most patients; some patients may tolerate even longer intervals, such as 96 hours (1366–1370).

In the United States, buprenorphine can be distributed not only in special clinics but also through clinicians' offices; access in this latter setting provides a means for expanding treatment

capacity and mainstreaming the care of opioid dependence. Daily sublingual maintenance doses typically fall between 8 and 32 mg. The buprenorphine-naloxone combination tablet significantly reduces the risk the medicine will be diverted for other uses because naloxone will exert a potent opioid antagonist effect if the combination tablet is crushed and administered intravenously by an opioid-dependent person. Details on use of the medication (e.g., induction, withdrawal) are available through specific guidelines published by the Center for Substance Abuse Treatment and through courses sponsored by professional societies, including APA.

Buprenorphine is generally safe, and its side effects can be similar to those seen with full mu agonist opioids. However, in the context of abrupt cessation of opioid use, buprenorphine is associated with a comparatively mild withdrawal syndrome (126). Another notable difference from methadone is that overdose with buprenorphine generally does not produce significant respiratory depression (1371); this probably reflects buprenorphine's partial mu agonist effects. Nevertheless, there have been reports of fatalities when individuals overdose with a combination of buprenorphine and a benzodiazepine, typically when both are taken parenterally. These reports have come from France, where buprenorphine is used extensively for the outpatient treatment of opioid dependence and where prescribing benzodiazepines is also quite common. Finally, there is some evidence that buprenorphine may produce mild elevations in liver function tests, especially in individuals with a history of liver disease. This is more likely to occur if large amounts (greater-than-usual clinical doses) of buprenorphine are taken parenterally.

c) Opioid antagonist therapy: naltrexone

Naltrexone is an opioid antagonist that can be an alternative to maintenance on full or partial mu opioid agonists. By tightly binding to opioid receptors without producing a psychoactive effect, naltrexone blocks the pleasurable effects of the usual street doses of heroin and other opioids, thereby discouraging opioid use and diminishing conditioned craving. Naltrexone cannot be given to individuals while they are actively dependent on opioids because it can precipitate an immediate opioid withdrawal syndrome. Before starting naltrexone, patients must be completely withdrawn and abstinent for at least 5 days from a short-acting opioid such as heroin or 7 days from a longer-acting opioid such as methadone. A urine toxicology screen for opiate medication may be indicated before naltrexone therapy is initiated. The risk of relapse during the interval between opioid withdrawal and the initiation of naltrexone treatment is high; for this reason, rapid opioid withdrawal, using clonidine and naloxone, has been used to shorten the interval between withdrawal and initiation of naltrexone treatment. Repeated doses of naloxone, a short-acting opioid antagonist related to naltrexone, have also been used with clonidine to shorten opioid withdrawal.

After withdrawal and the appropriate period of abstinence, a test dose of 0.8 mg i.m. of naloxone can be used to determine that the individual is no longer dependent on opioids before naltrexone treatment is initiated. Naltrexone can be taken as a daily dose of 50 mg or, because of its long duration of action, three times per week with doses of 100 mg on Monday and Wednesday and 150 mg on Friday. Naltrexone is approved for the treatment of opioid dependence in the United States; it has no abuse potential and is not a scheduled substance.

Studies of naltrexone's efficacy are mixed. Although inpatient studies of naltrexone-treated, opioid-dependent individuals who were given the opportunity to self-administer opioids have shown that naltrexone is highly effective at attenuating opioid use (1372), outpatient clinical trials have failed to demonstrate a similar robust effect (1373). Patients often drop out of such studies shortly after completing opioid withdrawal and starting on naltrexone. This is probably related, in part, to the absence of a psychoactive effect with naltrexone. In certain populations of motivated patients (e.g., patients on federal probation), however, naltrexone can be useful and effective (1374, 1375).

The adverse effects of naltrexone may include dysphoria, anxiety, and gastrointestinal distress. As previously noted, naltrexone can precipitate withdrawal in actively opioid-dependent individuals. Naltrexone's label notes that there is a risk that liver function test values will in-

crease for some patients, but a review of the evidence shows that these cases occurred only with higher daily doses of naltrexone (300 mg/day) or, in rare cases, in patients who were over age 40 years and on a dose of <300 mg/day (1376). Finally, after discontinuation of chronically administered naltrexone for the treatment of opioid dependence, there is an increased sensitivity to opioid effects and an increased risk that opioid overdose will lead to significant respiratory depression; this is likely related to the up-regulation of opioid receptors while a patient is being treated with naltrexone (1377).

2. Treating intoxication

The care of patients with an opioid use disorder is frequently complicated by episodes of relapse. Consequently, it is important in ongoing treatment to recognize and treat intoxication with opioids or other substances.

Mild to moderate opioid intoxication usually does not require treatment. An uncomplicated overdose with a short-acting opioid that has a relatively short half-life, such as heroin, may be treated in an emergency department, with release after a few hours. Overdose with longer-acting opioids such as methadone, however, requires closer inpatient observation for a minimum of 24–48 hours. In addition, severe opioid overdose, marked by respiratory depression, may be fatal and requires treatment in an emergency department or inpatient setting. Naloxone, an opioid antagonist, reverses respiratory and CNS depression as well as other manifestations of overdose. (Its use is described in detail in Section II.E.1.) A patient who deliberately takes an overdose as part of a suicide attempt requires thorough psychiatric evaluation typically in a hospital setting. For patients who do not require medical or psychiatric hospitalization, appropriate follow-up is a necessary part of discharge planning.

3. Treating withdrawal

An opioid-dependent individual may undergo opioid withdrawal rather than be maintained in methadone or buprenorphine treatment if, for example, the patient has a relatively short history of opioid abuse with a good prognosis for remaining abstinent without pharmacological maintenance, no maintenance treatment program is available locally, or the patient desires to not be restricted by the requirements of maintenance medication. Some patients successfully maintained on a medication such as methadone or buprenorphine will also want to undergo medically supervised withdrawal.

Criteria for withdrawing patients from long-term maintenance on methadone or buprenorphine include demonstrated progress toward a drug-free lifestyle, stability in personal and occupational adjustment, the absence of other substance use disorders, and successful treatment and remission of any co-occurring psychiatric disorders.

Precipitous discharge from maintenance programs and concurrent withdrawal of methadone are associated with a high rate of relapse to illicit opioid use, arrests, and death. Voluntary termination of methadone maintenance also carries a high risk of relapse, even for patients who have responded well to treatment. Patients who voluntarily discontinue maintenance treatment should receive supportive treatment during withdrawal as well as aftercare services to aid in maintaining abstinence. Patients who relapse repeatedly despite such support should be given the option of voluntary long-term maintenance on methadone or buprenorphine.

The goal of opioid tapering is to minimize acute withdrawal symptoms and help patients transition to long-term treatment for opioid dependence. The use of standard rating scales for withdrawal (e.g., Clinical Institute Narcotic Assessment) can help guide dosing in an objective and routine manner. Five pharmacological strategies are in general use: 1) methadone substitution, with gradual methadone tapering; 2) abrupt discontinuation of opioids, with use of clonidine to suppress withdrawal symptoms; 3) clonidine-naltrexone detoxification, where withdrawal symptoms are precipitated by naltrexone and then suppressed by clonidine; 4) bu-

prenorphine substitution, followed by abrupt or gradual discontinuation of buprenorphine; and 5) use of other medications to treat the symptoms of opioid withdrawal.

a) Use of methadone for withdrawal

Methadone hydrochloride is highly effective in ameliorating the symptoms of opioid withdrawal. Although the use of opioids to detoxify or maintain opioid-dependent patients requires special licensing (see Section II.H.3), this regulation is waived for inpatients admitted primarily because of a life-threatening general medical or psychiatric condition who also require methadone to stabilize their opioid dependence during the inpatient stay.

Inpatient opioid withdrawal with methadone involves stabilizing a patient on a daily methadone dose that is determined by the patient's response based on objective withdrawal signs (1378, 1379). Once the stabilization dose is determined (usually 40–60 mg/day and sometimes less), methadone can be tapered, for example, by increments of 5 mg/day. In inpatient settings, detoxification from heroin or other short-acting opioids can usually be completed within 7 days, but a more gradual tapering will result in a smoother clinical course.

When compared with inpatient withdrawal, outpatient opioid withdrawal uses a higher initial dose of methadone and occurs over a longer period of time. The goal of using a higher initial dose of methadone is to help dependent individuals end illicit opioid use. Because studies have suggested that slow tapers are associated with better outcomes, methadone should be tapered gradually over a period of weeks. Many patients tolerate methadone reductions to 20–30 mg/day with little difficulty, but further dose reductions may lead to increasing withdrawal distress. Even with gradual reductions in the dose, such distress may be difficult for some patients to tolerate and may be accompanied by high dropout and relapse rates during this later phase of withdrawal.

b) Use of clonidine for withdrawal

Clonidine is a centrally acting α_2-adrenergic antihypertensive medication that effectively decreases the noradrenergic hyperactivity associated with opioid withdrawal. Clonidine is not approved for opioid withdrawal in the United States but has been extensively studied and used for this indication elsewhere. Clonidine reduces withdrawal symptoms such as nausea, vomiting, diarrhea, cramps, and sweating but, unlike methadone, does little to reduce other symptoms such as muscle aches, insomnia, distress, and drug craving (1380, 1381). As a nonopioid medication, clonidine has some advantages over methadone for withdrawal. For example, clonidine does not produce opioid-like tolerance or dependence or the postmethadone rebound in withdrawal symptoms (1382). In addition, patients completing a course of clonidine-assisted withdrawal can immediately be given an opioid antagonist (e.g., naltrexone) if indicated. The disadvantages of clonidine include its aforementioned inability to improve certain opioid withdrawal symptoms, associated hypotension that can be profound despite the use of low doses of this medication, and its possible sedative effects. Contraindications to the use of clonidine include acute or chronic cardiac disorders, renal or metabolic disease, and moderate to severe hypotension (1383).

On the first day of clonidine-aided detoxification, a clonidine dose of 0.1 mg three times daily (totaling 0.3 mg per 24 hours) is usually sufficient to suppress signs of opioid withdrawal; inpatients can generally receive higher doses to block withdrawal symptoms because of the availability of medical staff to monitor the patient for hypotension and sedation. The dose is adjusted until withdrawal symptoms are reduced. If the patient's blood pressure falls below 90/60 mm Hg, the next dose should be withheld, after which tapering can be resumed while the patient is monitored for signs of withdrawal. In the case of short-acting opioids such as heroin, clonidine-aided withdrawal usually takes 4–6 days. Other medications may be used along with clonidine to treat withdrawal symptoms.

In general, clonidine-assisted detoxification is easier to carry out and monitor in inpatient settings. Clonidine-induced sedation is also less of a problem for inpatients. However, when

delivered by experienced staff, outpatient detoxification with clonidine is a reasonable approach (1384–1386). Outpatients should not be given more than a 3-day supply of clonidine for unsupervised use because treatment requires careful dose titration and clonidine overdoses can be life-threatening (1387, 1388).

Clonidine can be an effective alternative to methadone for treating opiate withdrawal; the completion rate for clonidine-treated outpatients is relatively low and roughly comparable to that of methadone withdrawal (1387, 1389).

c)   Use of clonidine-naltrexone for rapid withdrawal

The combined use of clonidine and naltrexone for rapidly withdrawing patients from an opioid has been demonstrated to be safe and effective. Essentially, naltrexone-precipitated withdrawal is avoided by pretreating the patient with clonidine. This technique is most useful for opioid-dependent patients who are in transition to narcotic antagonist treatment. The limitations of this method include the need to monitor patients for 8 hours on the first day because of the potential severity of naltrexone-induced withdrawal and the need for careful blood pressure monitoring during the entire detoxification procedure. However, relapse rates with naltrexone maintenance are high.

A related technique is to withdraw a patient from an opioid while the patient is maintained under general anesthesia. This technique has been called ultra-rapid opioid detoxification and has included naltrexone maintenance after the acute withdrawal is completed. Although some small uncontrolled studies have reported good long-term outcomes with this method, it appears to be no more effective than methadone detoxification in achieving beneficial outcomes such as maintenance of abstinence (1390). In addition, complications associated with such rapid withdrawal procedures (e.g., general anesthesia) coupled with the lack of better long-term results suggest that the procedure should not be commonly used (1390).

d)   Use of buprenorphine for withdrawal

Prior to buprenorphine's approval in the United States for the treatment of opioid dependence, there were reports of the efficacy and safety of its analgesic form when used for medically supervised opioid withdrawal. Clinicians used parenteral buprenorphine for relatively short opioid withdrawal (≤1 week), administered by injection or provided in the liquid (analgesic) form sublingually. Now with FDA approval of the sublingual form of this medication, the analgesic form for opioid withdrawal should no longer be used, and this nonapproved use of injectable buprenorphine is not recommended.

Studies of buprenorphine for opioid withdrawal have generally found that it has greater patient acceptability and is more effective than clonidine (1384, 1391–1393), with the two medications differing on measures of subjective symptoms of opioid withdrawal. Well-designed and executed studies comparing buprenorphine to methadone for the treatment of opioid withdrawal have not been published.

When buprenorphine is used for inpatient opioid withdrawal, patients can be stabilized on a relatively low dose of daily sublingual buprenorphine (e.g., 8 mg/day), with the goal of suppressing opioid withdrawal symptoms. Both tablet forms (with or without naloxone) can be used in an inpatient setting, as the risk of diversion and parenteral abuse is low. The dose can be decreased in increments of 2 mg/day over several days. Because buprenorphine has a long duration of action, minimal withdrawal symptoms are seen during the dose reduction. However, some clinicians report that withdrawal symptoms can appear several days after the last dose of buprenorphine, after a patient is discharged from an inpatient setting.

If buprenorphine is used for the outpatient treatment of opioid withdrawal, then procedures similar to those described earlier for methadone should be followed. But the tablet form combined with naloxone is preferred. For example, patients should be initially stabilized on a daily dose (probably 8–32 mg/day) of buprenorphine that suppresses opioid withdrawal and results

in abstinence from illicit opioid use. Dose reductions should then occur gradually over a period of 10–14 days. Because buprenorphine tablets are not scored, the smallest dose increment reduction possible is 2 mg.

It should be emphasized that concurrent nonpharmacological treatments should be used to maximize the likelihood of maintaining abstinence throughout and after withdrawal. However, long-term outcomes associated with withdrawal are generally poorer than those seen with maintenance treatments (1394).

e) Use of other medications

Some clinicians and treatment programs have used medications targeting the symptoms of opioid withdrawal as the primary means for treating this condition. For example, sedative-hypnotics or anxiolytics are used to treat insomnia and/or anxiety, antiemetics are prescribed to treat nausea and vomiting, NSAIDs are provided for muscle cramps, and antispasmodics are used to treat gastrointestinal cramping. There are limited controlled data about the use of such medications for the treatment of opioid withdrawal. Some psychiatrists maintain that the abuse potential of sedative-hypnotics and anxiolytics is too great to be used with these patients and that these medications may also precipitate craving for opioids and relapse. Others feel that for carefully selected patients and with appropriate monitoring, the use of benzodiazepines over a relatively brief period (i.e., 1–2 weeks) may be helpful in ameliorating the often debilitating insomnia that can accompany opioid withdrawal (1395). Diphenhydramine, hydroxyzine, and sedating antidepressants (e.g., doxepin, amitriptyline, trazodone) have also been used for this purpose. It should be noted that these medications have also been abused, although much less often than benzodiazepines (129). Other medications such as NSAIDs and antispasmodics may be safely provided but appear to be less effective than mu agonist opioids for symptom relief.

▶ D. PSYCHOSOCIAL TREATMENTS

When considering psychosocial treatments for treating opioid-related disorders, it is essential to note that all clinical trials of psychosocial interventions for opioid abusers have taken place in programs that also provide either opioid agonist maintenance (e.g., methadone) or treatment with opioid antagonists. Although some follow-up studies of naturalistic treatment have found equivalent efficacy for methadone maintenance and outpatient drug-free programs for heroin users (61, 1396–1398), early attempts at providing psychotherapy alone yielded unacceptably high attrition rates (1399).

1. Cognitive-behavioral therapies

In individuals who are receiving methadone maintenance, CBT is efficacious in reducing illicit substance use and achieving a wide range of other treatment goals. The benefits of CBT in combination with drug counseling are equivalent to those of drug counseling alone or drug counseling plus supportive-expressive psychotherapy in patients with low levels of psychiatric symptoms; however, in the presence of higher degrees of depression or other psychiatric symptoms, supportive-expressive therapy or CBT has been shown to be much more effective than drug counseling alone (177, 218, 531, 1400, 1401). CBT may also help reduce other target symptoms or behaviors (e.g., HIV risk behaviors) in opioid-using individuals (1402). Group-based relapse prevention therapy, when combined with self-help group participation, may also help recently detoxified patients reduce opioid use and criminal activities and decrease unemployment rates (1403).

2. Behavioral therapies

Contingency management approaches are beneficial in reducing the use of illicit substances in opioid-dependent individuals who are maintained on methadone (170, 195, 1295). Although other reinforcers or rewards (e.g., vouchers for movie tickets or sporting goods) may be provided to patients who demonstrate specified target behaviors (e.g., providing drug-free urine specimens, accomplishing specific treatment goals, attending treatment sessions), methadone take-home privileges are a commonly offered and effective incentive that is made contingent on reduced drug use (197–199, 202). Furthermore, contingency management, either alone or in conjunction with family therapies, can also be used to enhance adherence with unpopular treatments such as naltrexone and has been shown to result in diminutions in drug use among recently detoxified opioid-dependent individuals (165–167, 1404–1407).

3. Psychodynamic and interpersonal therapies

The utility of adding a psychodynamic therapy to a program of methadone maintenance has been investigated. The provision of supportive-expressive therapy, a specific approach to such treatment, may be particularly helpful for patients with high levels of other psychiatric symptoms (177, 218) (see Section VII.D.1). However, in terms of individual IPT, the potential benefits of treatment are unclear, as it is very difficult to engage opioid-dependent patients in such approaches. Psychodynamically oriented group therapy, modified for substance-dependent patients, appears to be effective in promoting abstinence when combined with behavioral monitoring and individual supportive psychotherapy (1301).

4. Family therapies

Family therapy has been demonstrated to enhance treatment adherence and facilitate implementation and monitoring of contingency contracts with opioid-dependent patients (1408, 1409). Family therapies are described in detail in Section II.F.8.

5. Self-help groups and 12-step-oriented treatments

Self-help groups, such as Narcotics Anonymous, are beneficial for some individuals in providing peer support for continued participation in treatment, avoiding substance-using peers and high-risk environments, confronting denial, and intervening early in patterns of thinking and behavior that often lead to relapse. Because of the emphasis on abstinence in the 12-step treatment philosophy, patients maintained on methadone or other opioid agonists may encounter disapproval for this type of pharmacotherapy at Narcotics Anonymous meetings.

▶ E. CLINICAL FEATURES INFLUENCING TREATMENT

The treatment implications of various clinical features are summarized in Section II.G. In addition to these considerations, specific sequelae and patterns of co-occurring disorders need to be considered for patients with an opioid use disorder.

1. Use of multiple substances

Dependence on alcohol, cocaine, or other substances of abuse is a frequent problem for opioid-dependent patients. In one study, cocaine abuse was found to occur in about 60% of patients entering methadone programs (169). In studies of opioid-dependent patients in active treatment, rates of cocaine use as high as 40% or more have been reported (1410–1413). Similarly, heavy drinking is a problem for an estimated 15%–30% of methadone-maintained patients, and benzodiazepine abuse may be just as common in this population (1414, 1415). Comparable data regarding rates of co-occurring substance use disorders in patients treated in naltrexone programs are not generally available.

Other co-occurring substance use disorders require special attention because treatment directed at opioid dependence alone is unlikely to lead to the cessation of other substance use. Treatment is generally similar to that described for individual substances elsewhere in this practice guideline. Increased frequency of behavioral monitoring (e.g., daily breath or semiweekly urine toxicology testing), intensified counseling, contingency contracting, referral to specific self-help groups (e.g., AA), and specialized pharmacological treatments (e.g., disulfiram) have all been used with varying degrees of success. The results of two studies suggest that higher methadone doses coupled with intensive outpatient treatment may decrease cocaine use by methadone-maintained patients (1416).

Opioid-dependent patients who are also dependent on other substances, particularly CNS depressants, should be stabilized with methadone and then gradually withdrawn from the other substances. Efforts to abruptly eliminate all substances of abuse will not be successful with all patients. In such cases, the elimination of the drugs one at a time may be warranted.

The use of aversive contingencies, such as methadone dose reduction or even withdrawal, for continued abuse of cocaine (or sedatives or alcohol) for patients in methadone maintenance treatment is controversial. Some psychiatrists believe that requiring methadone withdrawal for persistent substance abuse causes many patients to cease or greatly limit use, whereas failure to enforce such limits implicitly gives patients license to continue use. Others believe that methadone withdrawal is never justified for patients abusing alcohol or other substances because of the proven efficacy of methadone in reducing intravenous heroin use, improving social and occupational functioning, and providing the opportunity to continue to motivate patients to reduce other substance use.

2. Psychiatric factors

The reduction of opioid use in patients with a preexisting co-occurring psychiatric disorder may precipitate the reemergence of previously controlled psychiatric symptoms (e.g., depression, mania, psychosis), which in turn may increase the risk of relapse to substance use (1417).

In prescribing medications for co-occurring non-substance-related psychiatric disorders, psychiatrists should be alert to the dangers of medications with a high abuse potential and to possible drug-drug interactions between opioids and other psychoactive substances (e.g., benzodiazepines) (442, 1378, 1400). For example, the use of MAOIs should be avoided because of their potential interaction with alcohol, cocaine and other stimulants, and opioids, including meperidine and dextromethorphan. In general, benzodiazepines with a rapid onset, such as diazepam and alprazolam, should also be avoided because of their abuse potential (1418). However, benzodiazepines with a slow onset and substantially lower abuse potential (e.g., oxazepam, clorazepate) can probably be used safely for selected patients to, for example, ameliorate insomnia (Section VII.C.3.e), provided that appropriate controls are applied (1419). With all other psychotropic medications, decisions about prescriptions should consider that patients may not take medications as prescribed; random blood or urine monitoring can sometimes help in determining adherence.

3. Comorbid general medical disorders

The injection of opioids may result in the sclerosing of veins, cellulitis, abscesses, or, more rarely, tetanus infection. Other life-threatening infections associated with opioid use by injection include bacterial endocarditis, hepatitis, and HIV infection. HIV infection rates have been reported to be as high as 60% among individuals dependent on heroin in some areas of the United States (see DSM-IV-TR, p. 275). Counseling on how to reduce HIV risk should be a routine part of treatment for intravenous opioid users (559).

Tuberculosis is a particularly serious problem among individuals who inject drugs, especially those dependent on heroin. Infection with the tubercle bacillus occurs in approximately 10% of these individuals. For non-HIV-infected patients who test positive for the purified protein

derivative of tuberculin, the lifetime risk of developing active tuberculosis is approximately 10% and the 1-year risk is 7%–10% (1420). Guidelines regarding prophylactic treatment for patients with a positive skin test have been published (1421).

As described in DSM-IV-TR (p. 275), in addition to the presence of life-threatening infections, opioid dependence is associated with a death rate as high as 1.5%–2% per year from overdose, accidents, injuries, or other general medical complications.

4. Pregnancy

In addition to the general effects of substance use during pregnancy (Section II.G.4), opioid use disorders may have adverse effects on the health of the pregnant woman, the course of the pregnancy, fetal and early child development, and parenting behavior. In pregnant women these effects include 1) poor nourishment, with accompanying vitamin deficiencies or iron- and folic acid-deficiency anemias; 2) general medical complications from frequent use of contaminated needles (abscesses, ulcers, thrombophlebitis, bacterial endocarditis, hepatitis, urinary tract infections, and HIV infection); 3) sexually transmitted diseases (gonorrhea, chlamydia, syphilis, herpes); and 4) hypertension.

Possible effects of opioid use and the related lifestyle on the course of the pregnancy include preeclampsia (toxemia), miscarriage, premature rupture of membranes, and infections. Possible short- and long-term effects on the infant include low birth weight, prematurity, stillbirth, neonatal abstinence syndrome, and sudden infant death syndrome (1327, 1422, 1423). Approximately 50% of the infants born to women with opioid dependence are physiologically dependent on opioids and may experience a moderate to severe withdrawal syndrome requiring pharmacological intervention. However, when socioeconomic factors (e.g., family disruption, poverty) are controlled for, mild to moderate neonatal withdrawal does not appear to affect psychomotor or intellectual development (1423).

The goals of treatment for the pregnant opioid-using patient include ensuring physiological stabilization and avoidance of opioid withdrawal; preventing further substance abuse; improving maternal nutrition; encouraging participation in prenatal care and rehabilitation; reducing the risk of obstetrical complications, including low birth weight and neonatal withdrawal, which can be lethal if untreated; and arranging for appropriate postnatal care when necessary.

Pregnant patients who lack the motivation or psychosocial support to remain substance free should be considered for methadone maintenance regardless of their treatment history, as methadone maintenance improves infant outcomes relative to continued maternal heroin use (1424–1426). In a randomized comparison of enhanced and standard methadone maintenance for pregnant opioid-dependent women, Carroll et al. (1427) found that enhanced treatment—consisting of standard treatment (daily methadone medication, weekly group counseling, and thrice-weekly urine screening) plus weekly prenatal care by a nurse-midwife, weekly relapse prevention groups, positive contingency rewards for abstinence, and the provision of therapeutic child care during treatment visits—resulted in improved neonatal outcomes (longer gestations and higher birth weights) but did not affect maternal substance use. Contingency management approaches may also be implemented to enhance adherence (1299, 1428, 1429). Withdrawal from methadone is not recommended, except in cases where methadone treatment is logistically not possible. In cases where medical withdrawal is necessary, there are no data to suggest that withdrawal is worse during any one trimester.

Although the long history of methadone use in pregnant women makes this medication the preferred pharmacotherapeutic agent, a growing body of evidence suggests that buprenorphine may also be used. Jones et al. (1430), in a randomized, double-blind, double-dummy, flexible-dosing, parallel-group controlled trial, compared 4–24 mg/day sublingual buprenorphine to 20–100 mg/day oral methadone, with treatment starting in the second trimester of pregnancy. Although the study was limited by its small sample size, buprenorphine and methadone showed comparable outcomes in terms of neonatal abstinence syndrome. Data from uncon-

trolled observations in more than 300 neonates also suggest that buprenorphine may be useful in pregnant women, with rates of neonatal abstinence syndrome possibly less than those observed with methadone treatment during pregnancy (1431).

Data on other treatments for opioid withdrawal or dependence during pregnancy are sparse. In particular, data on the safety of clonidine in pregnant patients are not available. However, a narcotic antagonist should never be given to a pregnant substance-using patient because of the risk of spontaneous abortion, premature labor, or stillbirth.

PART B

BACKGROUND INFORMATION AND REVIEW OF AVAILABLE EVIDENCE

VIII. DISEASE DEFINITION, NATURAL HISTORY AND COURSE, AND EPIDEMIOLOGY

▶ A. DISEASE DEFINITION AND DIAGNOSTIC FEATURES

As delineated in DSM-IV-TR, substance-related disorders are divided into two groups: substance use disorders, which include substance dependence and substance abuse, and substance-induced disorders, which include substance intoxication, substance withdrawal, substance-induced delirium, substance-induced persisting dementia, substance-induced persisting amnestic disorder, substance-induced psychotic disorder, substance-induced mood disorder, substance-induced anxiety disorder, substance-induced sexual dysfunction, and substance-induced sleep disorder. This section of the guideline focuses on the first group, substance use disorders.

1. DSM-IV-TR criteria for substance dependence and abuse

The DSM-IV-TR criteria for substance dependence, which are applicable to each of the substances described in this guideline, include cognitive, behavioral, and physiological signs and symptoms indicating ongoing substance use despite significant problems associated with such use. Usually this continuous use will result in tolerance, withdrawal, and a pattern of compulsive use. Table 2 lists the specific DSM-IV-TR criteria for substance dependence. Individuals who meet DSM-IV-TR criteria for substance abuse have not experienced signs or symptoms of withdrawal or tolerance or met the criteria for compulsive substance use required for a diagnosis of substance dependence. However, they have shown a maladaptive pattern of substance use that is associated with significant recurring adverse consequences. The specific DSM-IV-TR criteria for substance abuse are delineated in Table 1. With DSM-IV-TR criteria, patients may be classified as currently manifesting a pattern of abuse or dependence or as being in remission. Those in remission can be divided into six subtypes—full, early partial, sustained full, sustained partial, on agonist therapy, and in a controlled environment—on the basis of whether any of

the criteria for abuse or dependence have been met and over what time frame. Patients receiving agonist therapy (e.g., methadone maintenance) or living in a controlled substance-free environment are also categorized as being in remission, with the corresponding diagnostic modifier used to denote the circumstances of remission.

DSM-IV-TR includes nicotine dependence and nicotine withdrawal as disorders. Nicotine abuse is not included because clinically significant psychosocial problems from tobacco use are rare unless dependence is also present (1432); nicotine intoxication is also not included because it is very rare.

2. Associated features of substance use disorders

a) Cross-sectional features

Patients presenting for treatment of a substance use disorder frequently manifest signs and symptoms of substance-induced intoxication or withdrawal. The clinical picture varies with the substance used, the dosage, the duration of action, the time elapsed since the last dose, the presence or absence of tolerance, and co-occurring psychiatric or general medical conditions. The expectations of the patient, his or her style of responding to states of intoxication or physical discomfort, and the setting in which intoxication or withdrawal is taking place also play a role.

Patients experiencing substance-induced intoxication generally manifest changes in mood, cognition, and/or behavior. Mood-related changes may range from euphoria to depression, with considerable lability in response to or independent of external events. Cognitive changes may include shortened attention span, impaired concentration, and disturbances of thinking (e.g., delusions) and/or perceptions (e.g., hallucinations). Behavioral changes may include wakefulness or somnolence and lethargy or hyperactivity. Impairment in social and occupational functioning is also common in intoxicated individuals.

Other cross-sectional diagnostic features commonly found in patients with a substance use disorder include those related to any co-occurring psychiatric or general medical disorders that may be present. Psychiatric disorders that are often found in such patients include conduct disorder (particularly the aggressive subtype) in children and adolescents (1433–1435), depression, bipolar disorder, schizophrenia, anxiety disorders, eating disorders, pathological gambling, antisocial personality disorder, and other personality disorders (470, 624, 1434, 1436–1444).

Examples of general medical problems that may be directly related to substance use include cardiac toxicity resulting from acute cocaine intoxication, respiratory depression and coma in severe opioid overdose, and hepatic cirrhosis after prolonged heavy drinking (559). General medical conditions frequently associated with opioid-dependent individuals who administer opioids by injection include subacute bacterial endocarditis, HIV infection, and hepatitis. Patients whose substance use disorder is accompanied by diminished self-care and/or high levels of risk-taking behavior are at increased risk of experiencing malnutrition, physical trauma, and HIV infection (1445, 1446).

b) Longitudinal features

Patients with substance use disorders frequently present with a long history of repeated episodes of intoxication and withdrawal, interspersed with attempts to cease use of the substance. In patients who meet DSM-IV-TR criteria for substance abuse, episodes of intoxication may be sporadic and brief and rarely require general medical or psychiatric intervention; however, patients who meet DSM-IV-TR criteria for substance dependence often experience repeated episodes of intoxication that may last for weeks or months, interrupted by voluntary or involuntary periods of self-managed or medically managed withdrawal. Partial or complete withdrawal from abused substances may be followed by variable periods of self-imposed or involuntary (e.g., during periods of incarceration) abstinence, often ending in relapse to substance use and, eventually, resumption of dependence.

In some patients, dependence on a single substance may lead to use of and ultimately dependence on another substance (e.g., the development of alcohol dependence in patients already dependent on opioids or cocaine) (1447, 1448). These patients may replace one form of substance dependence with another.

Although many individuals who abuse alcohol or illicit substances maintain their ability to function in interpersonal relationships and in the work setting, substance-dependent patients presenting for treatment often have profound psychological, social, general medical, legal, and financial problems. These may include disrupted interpersonal (particularly family) relationships, absenteeism, job loss, criminal behavior, poor academic or work performance, failure to develop adaptive coping skills, and a general constriction of normal life activities. Peer relationships often focus extensively on obtaining and using illicit substances or alcohol. The risk of accidents, violence, and suicide is significantly greater for these individuals than for the general population (1449, 1450).

► B. NATURAL HISTORY AND COURSE

1. Nicotine dependence

About 33% of adults who smoke make a serious attempt to stop smoking each year (729). Over 90% of these attempts to quit are made without formal treatment (729). Among those who quit by their own efforts, 33% remain abstinent for only 2 days and 3%–5% remain abstinent for 1 year, after which little relapse occurs (746, 1451). Most smokers make several attempts to quit, and 50% of smokers eventually succeed in quitting (729). Smokers with a history of or current anxiety, depression, or schizophrenia are less likely to stop smoking (731, 760, 873, 1452). This could be due to several factors, including increased nicotine withdrawal or nicotine dependence, less social support, or fewer coping skills (760). Smokers who have current alcohol abuse or dependence are unlikely to stop smoking unless their alcohol-related problem resolves (1452). Whether alcohol or other substance abusers in recovery are less likely to stop smoking is unclear (1452).

About 50% of adults who attempt to stop smoking will meet DSM criteria for nicotine withdrawal (755). Smokers who have withdrawal-induced depression or severe craving are less likely to be successful in smoking cessation efforts (755, 760). In addition, fear of weight gain appears to be a major deterrent to cessation attempts, especially among women (771). The presence of cues for smoking is thought to be crucial in producing withdrawal; thus, withdrawal during inpatient stays on smoke-free units is often not as severe as expected (757).

2. Other substance use disorders

It is common for initial experiences with substance use to occur before puberty. At the earliest stages of use, experimenters or casual users who go on to develop a substance use disorder are generally indistinguishable from their peers with respect to the type and frequency of substance use. However, there is increasing evidence that individuals have differential vulnerability for the progression from use to abuse to addiction. This has led to a disease concept of addiction (4), including a neuronal basis for many of its clinical features (1453), the presence of genetic vulnerability (1454), and a characteristic chronic, relapsing course that resembles that of many medical disorders. However, because substance use disorders are frequently viewed as purely behavioral problems, many adolescents with these disorders are managed by their parents, school authorities, or the judicial system rather than being treated in specialized adolescent substance abuse treatment programs. The problem is further complicated by the lack of substance abuse treatment programs for adolescents, even in the private sector.

In adolescents, growing preoccupation with substance use, frequent episodes of intoxication, use of substances with greater dependence liability (e.g., opioids, cocaine), and a preference for routes of administration that result in quicker onset of the substance's effects (e.g., injection) and for more rapidly acting preparations (e.g., crack cocaine) presage the development of substance dependence. Although in most cases the onset of a substance use disorder occurs in the late teens and early 20s, some individuals begin abusing substances in mid- to late adulthood (948, 1455, 1456).

TABLE 5. Estimated Drug Use and Dependence Among 15- to 45-Year-Olds in the United States

	Estimated Cumulative[a] Occurrence of Extra-medical[b] Drug Use (%)	Estimated Cumulative Occurrence of Drug Dependence (%)	Estimated Proportion Becoming Dependent, Once Use Has Occurred (%)
Tobacco	75.6	24.1	31.9
Cocaine	16.2	2.7	16.7
Heroin	1.5	0.4	23.1
Alcohol	91.5	14.1	15.4
Cannabis	46.3	4.2	9.1

Source. Anthony et al. (1168).
[a]"Cumulative" to age at the time of assessment.
[b]"Extra-medical" refers to drug use outside the boundaries of what is prescribed.

Although the use of multiple substances often continues throughout adolescence, some individuals settle on a "drug of choice" early on. A preference for a particular substance is shaped by a variety of factors, including current fashion, availability, peer influences, and individual biological and psychological factors. Sex-specific differences in substance preference (e.g., heroin use in male users, sedative-hypnotic and benzodiazepine use in females) have diminished somewhat over the last two decades. Although substance abuse and dependence appear to aggregate in families, which would support a genetic influence (1457), some of this effect may be explained by the concurrent familial distribution of antisocial personality disorder, which may predispose individuals to the development of these disorders. On the other hand, genetic factors do affect the risk of developing alcohol dependence, particularly in male alcohol users with male biological relatives who are also alcohol dependent (1458–1459) and, to a lesser extent, in female users with a strong family history of the disorder (1460–1462).

Although there is considerable heterogeneity among patients with substance use disorders, the disease course is often chronic, lasting for years. Periods of sustained use are interrupted by periods of partial or complete remission. Although some individuals are able to achieve prolonged periods of abstinence without formal treatment, abstinence or periods of greatly reduced substance use are more likely to be sustained by patients who are able to maintain active participation in formalized treatment and/or self-help groups (e.g., AA) (43, 289, 1463–1465). Patients who experience a severe life crisis (e.g., loss of an important relationship, incarceration, serious general medical sequelae of substance use) are generally more motivated to seek treatment, but most still require external support to maintain their motivation to continue in treatment beyond the initial stages (e.g., detoxification).

During the first several years of treatment, most substance-dependent patients continue to relapse, although with decreasing frequency. Risk of relapse is higher in the first 12 months after the onset of a remission (8). Many patients experience several cycles of remission and relapse before they conclude that a return to "controlled" substance use is not possible for them. Regardless of the treatment site or the modalities used, the frequency, intensity, and duration of treatment participation are positively correlated with improved outcome (356).

In one sample of alcoholic individuals followed for 60 years, of those who remained abstinent for 2 years, almost 90% were still substance free at 10 years, and those who remained

substance free for 10 years had a very high likelihood (i.e., >90%) of being substance free at 20 years (9, 1465–1467). Prolonged abstinence, accompanied by improvement in social and occupational functioning, is more apt to occur in those who have lower levels of premorbid psychopathology, demonstrate the ability to develop new relationships, and consistently make use of self-help groups (e.g., AA) (9, 1464, 1468).

▶ C. EPIDEMIOLOGY

By any measure, substance use disorders constitute a major public health problem, costing the United States in excess of $400 billion annually, including the costs of treatment, related health problems, absenteeism, lost productivity, drug-related crime and incarceration, and education and prevention efforts (1469).

The motivation for using any psychoactive substance is, in part, related to the acute and chronic effects of these agents on mood, cognition, and behavior. In some individuals, the subjective changes (e.g., euphoria, tension relief) that accompany substance intoxication are experienced as highly pleasurable and lead to repetitive use. The proportion of users who eventually meet criteria for dependence varies according to substance (1168). Table 5 shows the percentage of adults who have used a particular substance and the risk of becoming dependent.

Thus, 31.9% of individuals who ever used tobacco developed dependence, and 16.7% of individuals who ever used cocaine developed dependence. This does not imply that nicotine pharmacology is twice as potent as cocaine. Indeed, laboratory studies (1470) show that cocaine has the most powerful reinforcing effects of any abused substance. In U.S. society, however, where nicotine is a widely available, legal drug with strong marketing to young people in movies and the media, the net effect is a high risk of dependence.

Given these significant rates of substance use disorders, it is not surprising that there is a considerable need for treatment of substance use disorders. For example, in the National Comorbidity Survey Replication (1471), about 67% of individuals with an alcohol or other substance use disorder did not receive even minimally adequate mental health specialty services, with even a lower portion receiving minimally adequate health care services. As another example, it was estimated that 2.3 million U.S. youth ages 12–17 years needed substance abuse treatment in 2004 (1472). Of these, 185,000 received treatment, leaving a gap of an estimated 2.1 million untreated adolescents nationwide. Although this gap is partly due to the failure of youths to recognize that they have a problem or their reluctance to disclose information to their parents and guardians, it is mostly attributable to the inadequacy of the health care system in addressing the needs of individuals who require treatment for a substance use disorder.

Substance use disorders are associated with a significant increase in morbidity and mortality, particularly among men. Each year non-nicotine-related substance dependence is, directly or indirectly, responsible for at least 40% of all hospital admissions and approximately 25% of all deaths (500,000 per year) (1448, 1473, 1474). The total economic cost of substance use disorders was estimated to be $414 billion for 1995 (1469). This estimate includes substance use disorder treatment and prevention costs as well as other health care costs, costs associated with reduced job productivity or lost earnings, and other costs to society such as crime- and social welfare-related expenses (1469).

A significant portion of new HIV infections occur among users of intravenous drugs or individuals who have had sexual contact with such individuals, with high-risk sexual behaviors among injecting drug users being the biggest predictor of HIV infection in men and women (1475, 1476).

Substance use disorders also exert a profound impact on those who come into contact with affected individuals. For example, an estimated 13.6% of individuals age 12 years or older drove under the influence of alcohol at least once over a 1-year period (1191), and approxi-

mately half of all highway fatalities involve a driver or pedestrian who is intoxicated (1477–1479). Similarly, more than half of all cases of domestic violence occur under the influence of alcohol or illicit substances (1476, 1479), and evidence from a broad range of studies suggests that alcohol may play a role in enhancing the possibility of domestic violence (1479). In addition, estimates based on urine testing in general populations suggest that 7.5%–15.0% of all pregnant women had been recently exposed to substances of abuse (excluding alcohol) at the time they first sought prenatal care (1480–1482). Although heavy use of alcohol was reported by <1% of pregnant women in the 2003 National Survey on Drug Use and Health (1191), 9.8% reported using alcohol and 4.1% reported binge drinking in the month before the survey.

Finally, substance use disorders are frequently associated with other forms of psychopathology. The lifetime prevalence of comorbid axis I psychiatric disorders in individuals with substance use disorders (including those with alcohol dependence or abuse) is 20%–90%, depending on the population screened and the rigor of the diagnostic criteria used, with treatment-seeking patients being at the higher end of the range (344, 426, 427, 1308, 1448, 1483–1486). Approximately 33% of hospitalized psychiatric patients manifest a co-occurring non-nicotine-related substance use disorder (10, 1487).

1. Nicotine dependence

Smoking has been labeled the most important preventable cause of death and disease (1488–1490). It is responsible for 20% of all deaths in the United States (over 400,000 deaths/year), and 45% of smokers will die of a tobacco-induced disorder (901, 1490). Cigarette smoking causes multiple physical problems, including lung, oral, and other cancers (1491–1494); cardiovascular disease (1495, 1496); respiratory infections (1497); chronic obstructive pulmonary disease (1498); gastrointestinal disorders (1499); and maternal/fetal complications (751, 901, 923). Secondhand smoke causes death in thousands of nonsmokers and morbidity in children and other relatives of smokers (1500–1502). Although only about 5% of tobacco use is via cigars, pipes, or smokeless tobacco (770, 1191), these have also been linked to oral cancers as well as to other medical problems (901). Most of the tobacco-induced disorders appear to be due to the carcinogens and carbon monoxide in tobacco smoke, although nicotine itself might also cause health problems (804, 1503, 1504). Smoking cessation can dramatically reduce the risk of heart disease and cancer and stop the decline in lung function in those with chronic obstructive lung disease (1489, 1502, 1505).

Nicotine, a potent alkaloid in tobacco leaves, is the substance that produces tobacco dependence. Tobacco dependence usually begins with a decision in adolescence to begin smoking, which has lifelong consequences. The beginning of tobacco dependence, as with other substance dependencies, is influenced mostly by nonpharmacological, learned, or conditioned factors. Peer influence, social setting, personality, and genetics are all important in determining who begins and who continues to smoke. Twin studies have found that the heritability of smoking is as great as, if not greater than, that for alcohol dependence (1506, 1507). Some of the heritability of smoking is shared with and some is independent of that for alcohol dependence (1508, 1509). Although smoking usually precedes the onset of most psychiatric disorders, other psychiatric factors that may also predict initiation of smoking include use and abuse of substances other than alcohol, attention deficit disorders, and mood symptoms (760).

The strength of nicotine dependence relates to the efficiency with which the smoked drug is delivered to the brain, a person's ability to precisely control the nicotine dose depending on the way the cigarette is smoked, the frequency of cigarette smoking, and the multiple cues for cigarette use as well as the many positive reinforcing effects of nicotine (758). However, the severity of nicotine dependence via cigarette smoking can be illustrated by the fact that only 33% of self-quitters remain abstinent for 2 days and fewer than 5% are ultimately successful on a given quit attempt (746, 1451). Despite the strength of nicotine dependence, tobacco use by

adults has decreased in recent years. In contrast, levels of adolescent smoking have remained at about 6,000 more adolescents beginning to smoke each day (770, 1510, 1511). According to the 2003 National Survey on Drug Use and Health (1191), approximately 70 million Americans (or about 30% of those age 12 years or older) reported using a tobacco product in the previous month and smoking a mean of 13 cigarettes each day. About 60% of current smokers (corresponding to approximately 36 million individuals in the United States) met criteria for nicotine dependence. Young adults (ages 18–25 years) reported the highest rates of use, with approximately 40% having smoked a cigarette in the previous month. In a CDC report on adolescent tobacco use, 64% of respondents reported ever having smoked cigarettes, 28% reported having smoked on at least one day in the previous month, and 14% reported having smoked on at least 20 of the previous 30 days (1511). Of high school seniors who reported having smoked, 29% already reported symptoms that met criteria for nicotine dependence (1512). More than 50% of adolescents indicate that they experience withdrawal symptoms after an attempt to quit (1513). Male and female adolescents have comparable rates of smoking in contrast to the case in adults, in whom tobacco use is more frequent in men (1191).

The prevalences of tobacco use and nicotine dependence are significantly increased among individuals with another psychiatric disorder. For example, in the 2001–2002 National Epidemiologic Survey on Alcohol and Related Conditions (347), highly significant associations were found between nicotine dependence and specific axis I and II disorders. Furthermore, nicotine-dependent individuals with a co-occurring psychiatric disorder made up 7.1% of the population yet consumed 34.2% of all cigarettes smoked in the United States (347). Epidemiologic findings from Germany have shown similar increases in nicotine dependence among psychiatrically ill individuals (1514). (The clinical implications of these findings are reviewed in greater detail in Section III.H.2.)

2. Alcohol-related disorders

Alcohol, like tobacco, is a commonly used and widely available licit substance that significantly affects public health (1515). According to the 2004 National Survey on Drug Use and Health (1472), about 50% of respondents age 12 years or older reported having had at least one drink and >20% reported at least one episode of binge drinking (consuming five or more drinks on the same occasion) in the previous month. Heavy drinking, defined as consuming at least five drinks on the same occasion for at least 5 of the previous 30 days, was reported by 6.9% of the population over age 12 years in the United States (approximately 16 million people). Across age groups, rates of binge and heavy drinking increase through adolescence and young adulthood, peak at ages 21–25 years, and then gradually fall through the adult years. When compared with their non-college-attending peers, college students were more likely to report alcohol use, binge drinking, and heavy drinking. At later ages, however, those who had completed college were less likely to engage in binge or heavy drinking, although they were still more likely to report current alcohol use. With the exception of individuals ages 12–17 years, in whom equivalent proportions of current alcohol use are reported by both sexes, men are more likely to report drinking than women (62% vs. 46%). Although whites were most likely to report current alcohol use, rates of binge and heavy drinking were highest in American Indians/Alaskan Natives and Native Hawaiians or other Pacific Islanders. Binge and heavy drinking were lowest among Asians, with intermediate rates reported in blacks and Hispanics.

Demographic patterns in the 12-month prevalence of DSM diagnoses of alcohol abuse and dependence tend to parallel reported rates of binge and heavy drinking. For example, the 2001–2002 National Epidemiologic Survey on Alcohol and Related Conditions found a 12-month prevalence of alcohol abuse and dependence in the United States of 4.7% and 3.8%, respectively, with both abuse and dependence being more prevalent in whites, in male respondents, and in younger individuals (1516). In Europe, an epidemiological study in six countries using a different interviewing methodology (1517) found lower overall prevalences for alcohol

use disorders (4.1 and 1.1 lifetime and 0.7 and 0.3 12-month prevalences for alcohol abuse and alcohol dependence, respectively). However, demographic patterns were similar to those in the United States, with an increased prevalence of alcohol abuse and dependence observed in men and in those ages 18–24 years and a progressive decline in prevalence with increasing age.

There is some evidence that the demographic patterns of alcohol use disorders may be changing in the United States. As compared with nationally representative data obtained in the 1991–1992 National Longitudinal Alcohol Epidemiologic Survey, data from the 2001–2002 National Epidemiologic Survey on Alcohol and Related Conditions showed an overall increase in the prevalence of alcohol abuse, whereas the 12-month prevalence of alcohol dependence declined (1516). However, rates of alcohol dependence rose among male, young black female, and Asian male respondents. In addition, disproportionate increases in alcohol abuse were observed among female respondents and black and Hispanic youth (1516).

Although a DSM-IV-TR diagnosis of alcohol dependence takes precedence over a DSM-IV-TR diagnosis of alcohol abuse, and signs of alcohol abuse are sometimes used as an initial screen before inquiring about dependence, not everyone with alcohol dependence also meets criteria for alcohol abuse. Hasin and Grant (1518) found that 33.7% of respondents in the 2001–2002 National Epidemiologic Survey on Alcohol and Related Conditions with current alcohol dependence did not meet criteria for alcohol abuse. This finding was seen to a lesser extent among respondents with lifetime diagnoses of dependence, of whom 13.9% did not meet criteria for abuse. In terms of lifetime as well as current rates of alcohol use disorders, the presence of alcohol dependence without alcohol abuse was particularly common among women and among nonwhite populations.

Given the significant number of physical disorders that have been causally associated with alcohol use (1515), it is not surprising that the prevalence of alcohol use disorders is particularly high among general hospital inpatients. For example, Smothers et al. (1519), in a study of individuals admitted to nonfederal U.S. acute care general hospitals, found a 7.4% overall prevalence of a current alcohol use disorder and an estimated prevalence of 24% in those who had consumed at least 12 alcoholic drinks in the preceding 12 months, with approximately equal rates in men and women.

Use of alcohol, particularly binge or heavy drinking, is associated with greater rates of using tobacco or other substances. For example, in the 2003 National Survey on Drug Use and Health (1191), approximately 60% of heavy drinkers reported having smoked cigarettes in the previous month as compared with approximately 20% of those who were neither drinkers nor binge drinkers; approximately 33% of heavy drinkers reported using an illicit substance in the previous month, a rate that was 10-fold greater than in those who did not use alcohol. The increased association of alcohol and tobacco use disorders has also been noted longitudinally in follow-up assessments of subjects from the St. Louis Epidemiologic Catchment Area study (1520).

Rates of other psychiatric disorders are similarly increased in individuals with an alcohol use disorder. For example, mirroring the findings of earlier studies (1521–1523) and epidemiological data from Europe (1524), the National Epidemiologic Survey on Alcohol and Related Conditions (23) found that individuals meeting DSM-IV criteria for alcohol abuse were somewhat more likely to have a 12-month diagnosis of a mood or anxiety disorder (odds ratios 1.3 and 1.1, respectively). Furthermore, those meeting criteria for alcohol dependence had substantial increases in risk for a mood or anxiety disorder (odds ratios of 4.1 and 2.6, respectively) (23) as well as an increased likelihood of meeting diagnostic criteria for a personality disorder (1525). Such high rates of co-occurring disorders have important implications for the assessment and treatment of individuals with an alcohol use disorder (see Section IV.E.1).

3. Marijuana-related disorders

Marijuana is the most widely used illicit drug in the United States (1167) and worldwide. In the United States, a variety of studies suggest that the age at initial marijuana use has been low-

ering (1169). In the 2001 National Household Survey on Drug Abuse, more than 75 million (>34%) of Americans age 12 years or older reported having tried marijuana at least once and almost 19 million reported using it in the previous year (1167). It is estimated that 9%–10% of those who try marijuana will meet criteria for marijuana dependence at some time in their lives, and lifetime prevalence rates of marijuana have been estimated at 4% of the population (1168), making it the highest dependence rate of any illicit drug. Thus, although marijuana's relative dependence potential of 9% is lower than that of nicotine (32%), heroin (23%), cocaine (17%), or alcohol (15%), the large number of users will yield a high dependence rate in the population (1168). Although the overall prevalence of marijuana use remained stable from 1992 to 2002, the prevalence of marijuana abuse or dependence increased significantly during that time, with the greatest increases found among young black men and women and young Hispanic men (1170). Because the frequency and quantity of marijuana use have not changed, the increase in marijuana use disorders may be related to an increased potency of available marijuana (1170). Such increases in the prevalence of marijuana abuse and dependence may carry an added public health burden, given the increasing epidemiological evidence for adverse health consequences of marijuana use (1526–1528). In addition, rates of other substance use disorders (1529) and rates or symptoms of other psychiatric disorders may be increased among long-term marijuana users (1173, 1530–1535).

4. Cocaine- and other stimulant-related disorders

Although the prevalence of cocaine use has declined since the peak of the cocaine epidemic in 1980 (1536–1539), the 2003 National Survey on Drug Use and Health (1191) estimated that 2.3 million individuals (1.0% of the United States population) were current cocaine users in the United States, with 604,000 (0.3%) of those having used crack during the same 30-day period. Among eighth, tenth, and twelfth graders, the 30-day prevalence of cocaine abuse increased by more than twofold between 1991 and 1998, but during the 1990s the annual prevalence of cocaine use among high school seniors declined to 1%–2% (1539).

It is more typical for initial cocaine use to occur after age 18 years (1191), and cocaine-related disorders are most commonly found in individuals ages 18–30 years, with greater rates in men than women. Smoking of cocaine is associated with a more rapid progression from use to abuse or dependence than is intranasal use (1540, 1541).

An additional 1.2 million individuals in the United States use stimulants other than cocaine for nonmedicinal purposes (1191). Of special interest to psychiatrists is that the nonprescription use of methylphenidate increased among high school seniors from an annual prevalence of 0.1% in 1992 to 2.8% in 1997 and then remained at that level through 2003 (1539). In addition, localized epidemics of amphetamine and methamphetamine abuse have developed, particularly in the western and midwestern United States and more recently spreading to eastern U.S. cities (1542).

5. Opioid-related disorders

The Office of National Drug Control Policy estimates that 750,000 to 1,000,000 individuals are heroin dependent (1333a). However, heroin users constitute a small proportion of individuals using opiates for nonmedical purposes. Although rates of opiate dependence were not reported in the 2003 National Survey on Drug Use and Health (1191) and are difficult to ascertain (1543), the survey estimated that 31.2 million individuals (4.7% of U.S. population) had used narcotic pain-relief medication for nonmedical purposes in the previous month, most commonly combination medicines containing narcotic analgesics and acetaminophen (Vicodin, Lortab, Lorcet, Percocet, or Tylox) or aspirin (Percodan) (1191). Furthermore, there were statistically significant increases in the current and lifetime prevalence of nonmedical pain reliever use between 2002 and 2003 (1191).

IX. REVIEW AND SYNTHESIS OF AVAILABLE EVIDENCE

▶ ## A. NICOTINE DEPENDENCE

1. Somatic treatments

Pharmacotherapies for nicotine dependence can be divided into NRTs and nonnicotine medications. The following sections describe these therapies in terms of treatment goals, efficacy in smoking cessation, side effects, and implementation. For more information, the reader is referred to descriptive (602, 706, 750, 1544–1548) and meta-analytic (789, 790, 793, 795, 1549) reviews.

a) Nicotine replacement therapy

(1) Goals

The primary goal of NRT is to relieve withdrawal symptoms when patients stop smoking and thus allow them to focus on conditioning factors that typically trigger a relapse to smoking. After the acute withdrawal period, NRT is reduced gradually so that little withdrawal should occur. A secondary goal of NRT may be to reduce smoking, but this approach has not been well studied.

(2) Description of products

a. Nicotine transdermal patch

The nicotine transdermal patch takes advantage of the ready absorption of nicotine across the skin (799, 1550). It is available in four formulations: three 24-hour patches and one 16-hour patch for use while an individual is awake. Treatment initiation typically uses a 21- to 22-mg 24-hour patch or a 15-mg 16-hour patch. Patches are applied on the first morning of smoking cessation and then each morning thereafter. The nicotine is slowly absorbed so that on the first day venous nicotine levels peak 6–10 hours after administration. Thereafter, nicotine levels remain fairly steady, with a decline from peak to trough of 25%–40% with 24-hour patches (799). The 16-hour nicotine patches demonstrate similar nicotine pharmacokinetics after discontinuation of smoking. Nicotine levels obtained with the use of patches are typically half those obtained by smoking (799).

After 4–6 weeks, the nicotine patch dose is tapered to a middle dose (e.g., 14 mg/24 hours or 10 mg/16 hours) and then tapered again in 2–4 weeks to the lowest dose (7 mg/24 hours or 5 mg/16 hours). The recommended total duration of treatment is usually 6–12 weeks (71, 1550). Most, but not all, studies indicate abrupt discontinuation of the patch usually causes no significant withdrawal so that tapering may not be necessary (71). There are now two nicotine patches available over the counter: a 21-, 14-, and 7-mg strength patch (24-hour application) and a 22- and 11-mg strength patch (16-hour application). The 15-mg patch does not require tapering.

b. Nicotine gum

Nicotine ingested through the gastrointestinal tract is extensively metabolized on first pass through the liver (1551). In addition, nicotine is a gastrointestinal irritant that makes orally ingested nicotine an unpleasant treatment for patients who are already experiencing nicotine withdrawal. Nicotine gum (nicotine polacrilex) avoids this problem via buccal absorption

(1551). The gum, which is available as an over-the-counter medication, contains 2 or 4 mg of nicotine that can be released from a resin by chewing (886).

When compared with nicotine delivery via smoking, nicotine gum produces lower steady-state blood levels of nicotine and does not reach peak levels of nicotine absorption for >30 minutes (1551). Because cigarette nicotine is absorbed directly into the arterial circulation, arterial blood levels from smoking are 5–10 times higher than those from the 2- and 4-mg gum (1552). Venous nicotine levels from the 2- and 4-mg gum are about 33% and 67% of the steady-state (i.e., between cigarettes) levels of nicotine achieved by cigarette smoking, respectively (1551). Absorption of nicotine in the buccal mucosa and the resulting steady-state levels are further decreased by an acidic environment; thus, patients should not drink acidic beverages (e.g., coffee, soda, juice) immediately before, during, or after nicotine gum use (1552).

In terms of dosing, the original recommendation was to use one piece of 2-mg gum every 15–30 minutes as needed for craving. More recent work, however, suggests greater efficacy with scheduled dosing (e.g., 1 piece of 2-mg gum/hour) and 4-mg gum for highly nicotine-dependent smokers (724). Although the original recommended treatment duration was 3 months, many experts believe longer treatment is more effective. However, two trials of longer treatment durations produced contradictory results (801).

c.   Nicotine lozenges

The nicotine lozenge contains nicotine bound to a polacrilex ion-exchange resin, similar to the nicotine gum. It is available in 2- and 4-mg dose formulations. Because it does not have to be chewed, the lozenge may be preferable for smokers with dental problems or for those who do not like to chew gum. Compared with an equal dose of nicotine gum, the lozenge delivers 25% more nicotine (802). It is recommended that the lozenge be used every 1–2 hours for the first 2–4 weeks of treatment, with the frequency of use reduced to every 2–4 hours in subsequent weeks.

d.   Nicotine nasal spray

This type of NRT consists of a nicotine solution in a nasal spray bottle similar to those used with saline sprays and antihistamines (71, 809, 1553). Nasal sprays produce droplets that average 1 mg per administration (spray solutions are dispensed at 10 mg/ml); patients administer the spray to each nostril every 1–2 hours. This formulation produces a more rapid rise in and higher nicotine levels than the nicotine gum but less than that obtained with cigarettes. There is approximately a 30% replacement of plasma nicotine levels with nasal spray use (809). Peak nicotine levels occur within 10 minutes, and venous nicotine levels are about 67% of between-cigarette levels (782). Smokers are to use the product ad libitum up to 30 times/day for 12 weeks, including a tapering period.

e.   Nicotine vapor inhalers

Nicotine vapor inhalers are cartridges of nicotine containing about 1 mg of nicotine each placed inside hollow cigarette-like plastic rods. The cartridges produce a nicotine vapor when warm air is passed through them (805, 806). Absorption from the inhaler is primarily buccal rather than respiratory (1554). Nicotine blood levels produced by the nicotine vapor inhaler are about 33% of between-cigarette levels (1555). Smokers are instructed to puff continuously on the inhaler (0.013 mg/puff) during the day, with a recommended dose of 6–16 cartridges daily. The inhaler is to be used ad libitum for about 12 weeks.

(3)   Efficacy of nicotine replacement therapies

a.   General issues

In general, the various NRTs have shown comparable efficacy in studies using the rigorous outcome measure of at least 6 months of abstinence from smoking (790, 793, 1556). Although specific rates of smoking cessation vary across studies, there is typically a twofold increase in rates

of smoking abstinence with an NRT. Many studies have shown that NRTs decrease withdrawal symptoms such as anxiety, anger/irritability, depression, difficulty concentrating, and impatience in outpatient settings (602, 755); insomnia and weight gain, however, are not consistently decreased by all forms of NRT (801). For example, nicotine gum at 2 mg ad libitum appears less likely to reduce craving compared with the nicotine patch or nasal spray; however, this may be a dose-related issue, as the 4-mg gum does appear to better reduce craving (1557). Finally, higher doses of an NRT only marginally decrease withdrawal symptoms (801).

b. Nicotine transdermal patch

The overall efficacy of the nicotine transdermal patch for smoking cessation has been well documented. A 1994 meta-analysis of 17 randomized, placebo-controlled trials of the patch (71) documented abstinence rates of 27% vs. 13% at the end of treatment and 22% vs. 9% at 6-month follow-up for the nicotine and placebo patch, respectively. These effects of the nicotine transdermal patch were independent of patch type, treatment duration, tapering procedures, and behavioral therapy format or intensity, although it should be noted that behavioral treatment plus nicotine patch enhanced treatment outcomes compared with the patch alone. A recent meta-analysis of patch trials suggests an odds ratio of 1.81 (95% confidence interval [CI] = 1.63–2.02) for nicotine patch versus placebo patch treatment effects (790). Because the nicotine patch is available as an over-the-counter product, it is also noteworthy that randomized, double-blind, placebo-controlled studies (1549, 1558) as well as a meta-analysis (793) have demonstrated the efficacy of nicotine patch therapy in over-the-counter settings.

Several studies have addressed the issue of matching the patch dose to the patient's nicotine-dependence level, and there is modest evidence that higher patch doses are more helpful for more heavy and dependent smokers, at least with short-term outcomes. For example, Hughes et al. (1544) evaluated the effects of four doses of the patch (0, 21, 35, and 42 mg/day) for smoking cessation in 1,039 cigarette smokers using >30 cigarettes/day. In conjunction with weekly smoking cessation group therapy, patches were used daily for 6 weeks, after which the dose was tapered over an additional 10 weeks. At 12 weeks, there was a dose-dependent effect of nicotine patch therapy on smoking cessation rates, but it was less pronounced at 1-year follow-up. In an 8-week trial of 504 cigarette smokers using at least 15 cigarettes per day, Jorenby et al. (1559) compared two doses of the patch (44 and 22 mg/day) with three different intensities of counseling and found superior smoking cessation rates with the higher-dose patch only in combination with the minimal therapy condition and at the 4-week time point. Similar findings were reported by Killen et al. (1560) in their double-blind trial of 408 cigarette smokers who smoked >25 cigarettes per day. The subjects in that trial were randomized to receive either a high- (25-mg) or low- (15-mg) dose 16 hour/day patch for 6 weeks. Paoletti et al. (1561) stratified 297 cigarette smokers to a dose of patch based on low (≤250 ng/ml) or high (>250 ng/ml) baseline plasma cotinine levels and found comparable cessation rates for the 25- and 15-mg patches in individuals with high baseline plasma cotinine levels. Thus, further treatment studies are needed to determine if higher-dose patches are effective for heavier and more dependent smokers. In addition, evidence from one randomized, double-blind, placebo-controlled study suggests that nicotine patch therapy may improve smoking cessation outcomes even in individuals who had resumed smoking after previous nicotine patch treatment and were smoking at least 15 cigarettes per day (1562).

Other studies have assessed whether combining nicotine transdermal patch and other smoking cessation treatments results in improved outcomes. A randomized, double-blind, placebo-controlled trial by Bohadana et al. (1563) studied the efficacy of the nicotine inhaler in combination with a nicotine or placebo patch for up to 12 weeks in 400 nicotine-dependent subjects. The inhaler plus nicotine patch group had higher abstinence rates than the inhaler plus placebo patch group at 6 and 12 weeks but not at 6- or 12-month follow-up. These results suggest that the use of the nicotine patch can augment outcomes with the nicotine inhaler and

these two NRTs can be safely combined. The combination of nicotine patch with behavioral therapy has been studied in several trials. One trial suggested a modest additional benefit of nicotine patch at 10 weeks when combined with CBT (1564), but no difference was found at 6- and 12-month follow-ups. Two other trials (1559, 1565) used other behavioral interventions (e.g., self-help pamphlets, self-help video-enhanced manual, physician motivational messages, brief follow-up nurse visits, weekly cessation counseling groups) and found no augmenting effects of behavioral treatments over the nicotine patch alone.

Some studies have also shown efficacy for nicotine patch treatment in a variety of patient subgroups and specialized contexts. For example, a large double-blind, randomized, placebo-controlled study by Ahluwalia et al. (669) specifically examined the usefulness of the nicotine patch in African Americans, an important subset of the smoking population for which there is an insufficient number of studies assessing the efficacy of standard smoking cessation pharmacotherapies. Greater smoking cessation rates were observed with active patch (21 mg/day) relative to placebo patch at the end of the 10-week trial, with a trend toward significance at 6-month follow-up.

Three randomized, placebo-controlled trials have examined the efficacy of the nicotine patch in outpatient or hospitalized medical patients with smoking-related cardiac and pulmonary diseases. These trials demonstrated short- but not longer-term (i.e., >6 month) improvements in smoking cessation rates (910, 916, 1566). The negative outcomes, including mortality, were no greater with nicotine patch treatment than with placebo patch.

There have also been three preliminary controlled studies of the nicotine patch in patients with a psychiatric or substance use disorder. There have been two open-label studies of the patch (21 mg/day for 6 weeks, followed by 14 and 7 mg/day for 2 weeks each) for patients with co-occurring schizophrenia and nicotine dependence that demonstrated short-term smoking cessation in about 33% of patients (702, 703). In the study by George et al. (703), treatment of subjects with second-generation as compared with first-generation antipsychotics led to enhanced smoking cessation outcomes. However, in both studies there was a significant return to smoking in patients with schizophrenia 6 months after patch discontinuation. Finally, a single small, randomized, controlled trial in alcohol-dependent smokers (705) showed no significant effect of nicotine patch therapy on smoking cessation rates. Nevertheless, the patch was well tolerated by patients in all three studies. It is clear that placebo-controlled trials to establish the relative efficacy of the patch in psychiatric and substance-using populations are needed, but it appears that the patch has utility in treating smokers with a co-occurring psychiatric disorder.

c. Nicotine gum

Several placebo-controlled trials have established the safety and efficacy of nicotine gum for smoking cessation (790), with a pooled odds ratio of 1.66 (95% CI = 1.52–1.81). There is some evidence from randomized, controlled trials supporting the use of 4-mg nicotine gum in more highly dependent cigarette smokers (803, 1557, 1567, 1568). This finding supports the idea of matching the nicotine gum dose to the smoker's dependence level. The efficacy of matching gum dose to the patient's smoking dependence level appears to be independent of the intensity of behavioral therapy support, although this needs further study.

To manage the heavy smoker with treatment-resistant dependence, the combination of nicotine gum with nicotine patch is often used clinically, and its efficacy is supported by some evidence. For example, in a randomized trial of 374 nicotine-dependent cigarette smokers, Kornitzer et al. (888) found that the combination of active nicotine gum (2 mg) and active nicotine patch (15 mg/day) was superior to active patch plus placebo gum and placebo gum plus placebo patch at the end of the 12-week trial (34.2% vs. 22.7% vs. 17.3%) as well as at 1-year follow-up (18.1% vs. 12.7% vs. 13.3%).

d. Nicotine lozenges

Nicotine lozenges have been less well studied but also appear to be efficacious in improving short- and long-term smoking cessation rates. In a 6-week double-blind, randomized, placebo-controlled, multicenter study of 2- and 4-mg nicotine lozenges compared with placebo gum (802), smokers with low nicotine dependence (first cigarette >30 minutes after waking) were assigned to the 2-mg lozenge or placebo and those with a high nicotine dependence (first cigarette <30 minutes after waking) were assigned to the 4-mg lozenge or placebo. Both doses of the lozenge significantly increased carbon monoxide-verified continuous abstinence rates, with significant reduction in nicotine craving and withdrawal. At the 4-mg dose, abstinence rates were more than doubled (48.7% vs. 20.8%; p<0.001), suggesting that the higher 4-mg lozenge may be more efficacious in more highly dependent smokers and that the lozenge dose can be matched with the dependence level. The efficacy of the lozenge compared with placebo was also demonstrated at 12-month follow-up.

e. Nicotine nasal spray

Nicotine nasal spray has been found to be a safe and effective aid for smoking cessation in two randomized, double-blind, placebo-controlled trials (809, 1569). Both trials provided treatment for 3–6 months. Active nasal spray led to a doubling of quit rates during active use, but the differences between the active and placebo treatment were reduced or absent with extended follow-up, suggesting the need for maintenance use of this agent. The results of a recent Cochrane meta-analysis (790) suggested that the odds ratio for nicotine nasal spray versus placebo is 2.35 (95% CI=1.63–3.38). To date, long-term studies of the spray as well as studies of the spray in combination with the patch, gum, or bupropion have not been published.

f. Nicotine inhalers

Two randomized, double-blind, placebo-controlled trials (1570, 1571) have demonstrated the superiority of nicotine vapor inhalers to placebo inhalers for smoking cessation in trials of 4–6 months' duration, with two- to threefold increases in quit rates (17%–26%), compared with placebo at the trial endpoints, but smaller between-group differences at follow-up periods ≥1 year. The results of the Cochrane meta-analysis (790) suggest that the odds ratio for nicotine inhaler versus placebo is 2.14 (95% CI=1.44–3.18). Although these data support the short-term efficacy of the inhaler in cigarette smokers, longer-term trials are needed.

(4) Side effects of nicotine replacement therapies

a. Nicotine patch

No significant medical problems with nicotine patches have been found (798, 801, 1550, 1551). The most common minor side effects are skin reactions (50%), insomnia and increased or vivid dreams (15% with 24-hour patches), and nausea (5%–10%) (798, 801, 1550). Tolerance to these side effects usually develops within a week. In addition, the rotation of patch sites can decrease skin irritation, and a 24-hour patch can be removed before bedtime or changed to a 16-hour patch to determine if nicotine replacement is contributing to insomnia. Although the results of an early study suggested that the concomitant use of cigarettes and nicotine patches caused myocardial infarction (800), later analyses and prospective empirical studies in smokers with active heart disease indicated that the use of nicotine patches is safe in cardiac patients (836, 916). Abrupt cessation of the nicotine patch does not appear to produce significant withdrawal symptoms, and long-term use of the patch has not been associated with any long-term medical or psychiatric sequelae (140, 602, 798). There appears to be little dependence liability associated with patch use, as only 2% of patch users continue to use this product for an extended period after a cessation trial (796).

b. Nicotine gum

Major side effects from nicotine gum are uncommon and rarely deter use (790, 793, 804); minor side effects are of mechanical (e.g., difficulty chewing, sore jaw) or local pharmacological (e.g., burning in mouth, throat irritation) origin. Tolerance develops to most side effects over the first week (804). Education about the proper use of the gum (e.g., do not chew too vigorously) also decreases the side effects (804). In earlier research, some disorders were listed as contraindications to the use of nicotine gum (e.g., cardiovascular disease, pregnancy, hypertension). However, because nicotine blood levels are much lower with nicotine gum than with cigarettes, these contraindications have been removed (804, 1551).

The only potential psychological side effect of nicotine gum is the continuance of nicotine dependence (758). Abrupt cessation of nicotine gum can produce withdrawal symptoms similar to but less intense than that from cigarettes (758), whereas gradual reduction in the use of nicotine gum usually produces very minor or no withdrawal symptoms (758, 1572). There are several lines of evidence indicating that most long-term use is not dependence. Instead, long-term use appears to represent patients' desire to extend the duration of therapy based on their fear that they will return to smoking if they stop using the nicotine gum. West et al. (796) conducted a study on the continued use of NRT 15 weeks after smoking cessation and found that only 7% of smokers continued to use the gum after a cessation attempt compared with 2% continuing the patch and 10% continuing the nasal spray or inhaler. By 2 years, all but 1%–2% of smokers had stopped gum use, and the amount of gum use at long-term follow-up was minimal (usually 12 mg/day) (797). The potential harmful effects of long-term use of nicotine gum have not been studied; however, it is unlikely there are any, given the absence of exposure to carcinogens or carbon monoxide and the much lower levels of nicotine obtained from nicotine gum than from cigarettes (804, 1551).

c. Nicotine lozenges

Mild throat and mouth irritation have been reported in preliminary trials (802). Side effects of the nicotine lozenge include heartburn, hiccups, and nausea (802). In addition, because the lozenge contains phenylalanine, it should not be used by individuals with a history of phenylketonuria.

d. Nicotine nasal spray

The major short-term side effects of nicotine nasal spray are nasal and throat irritation, rhinitis, sneezing, coughing, and watering eyes (807–809). One or more of these occur in >75% of patients, although long-term nasal problems from use of nicotine nasal spray do not usually occur (807). Whether abrupt cessation of the spray produces withdrawal has not been studied. Nicotine nasal spray may have some potential to induce dependence. Several patients who quit smoking with nicotine nasal spray in some studies continued to use it for long periods (782, 811). Indeed, one controlled study of nicotine nasal spray by West et al. (796) determined that continued use of the spray occurred in 10% of smokers, and the results of a human laboratory study (811) suggest that nicotine nasal spray has modest reinforcing effects. Thus, follow-up of smokers using nasal spray is recommended.

e. Nicotine inhaler

No serious medical side effects have been reported with nicotine inhalers (810). About 50% of subjects report throat irritation or coughing (806). The results of the controlled study by West et al. (796) suggest that about 10% of smokers quitting with a nicotine inhaler continue to use it for extended periods, and thus follow-up of inhaler users is recommended.

(5) Implementation

Nicotine-dependent smokers benefit equally from nicotine gum, patch, inhaler, or nasal spray (790, 793, 1573, 1574). Some have suggested that NRT be used only if the patient is enrolled in behavioral therapy; however, the data clearly show that NRT is effective in the absence of behavioral therapy (790) and that not all individuals are receptive to concomitant behavioral therapy. Although nicotine gum and patches are available over the counter, psychiatrists may still encourage appropriate use of the patch consistent with package instructions, provide adjunctive psychiatric management and, when appropriate, psychosocial and other pharmacological therapies. It has been suggested that a patient's precessation blood level of cotinine, a metabolite of nicotine with a half-life of about 20 hours, may be a useful benchmark to examine the percent of nicotine replaced by NRTs (1575), presumably because the level from nicotine replacement is higher; however, this area is controversial and requires further study (1576).

Although most smoking cessation treatment lasts 6–12 weeks, some authors (71, 140, 602, 1577) have advocated longer-term use of NRT and even a nicotine replacement program. However, the European multicenter CEASE trial compared high (25-mg) versus low (15-mg) patch doses and shorter (22 weeks) versus longer (8 weeks) periods of treatment and found that although higher doses of the nicotine patch led to better outcomes, extending patch treatment beyond 8–12 weeks did not increase cessation rates (1578). In addition, a meta-analysis of nicotine patches did not find that longer treatment was associated with higher quit rates (71). However, no data examining whether longer NRT treatment is associated with higher abstinence rates are available for nicotine nasal spray, inhaler, or lozenges.

b) Sustained-release bupropion

(1) Goals

Bupropion is a first-line pharmacological treatment for nicotine-dependent smokers who want to quit smoking. It is a phenylaminoketone that is an atypical antidepressant and is available in immediate-release, sustained-release (SR), and extended-release (XR) formulations. Bupropion's mechanism of action in the treatment of nicotine dependence likely involves blockade of dopamine and norepinephrine reuptake (161) as well as antagonism of high-affinity nicotinic acetylcholine receptors (162). The goals of bupropion therapy entail cessation of smoking behavior, reduction of nicotine craving and withdrawal symptoms, and prevention of cessation-induced weight gain.

(2) Efficacy

Since the pivotal study by Hurt et al. (158) established the efficacy and safety of bupropion SR for treatment of nicotine dependence, which led to its FDA approval in 1998, multiple studies have confirmed its utility (160, 795, 812, 1579, 1580, 1582). A recent meta-analysis showed that rates of smoking cessation are doubled by bupropion treatment (795).

The 7-week double-blind, placebo-controlled multicenter trial of Hurt et al. (158) assigned 615 subjects who smoked 15 cigarettes per day to placebo or to 100, 150, or 300 mg/day bupropion SR; all treatment conditions also included weekly individual smoking cessation counseling. The end-of-trial, 7-week prevalence cessation rates were 19.0%, 28.8%, 38.6%, and 44.2%, respectively. At 1-year follow-up, the cessation rates were 12.4%, 19.6%, 22.9%, and 23.1%, respectively. In addition, bupropion SR treatment reduced weight gain associated with smoking cessation in a dose-dependent manner and significantly reduced nicotine withdrawal symptoms at the 150 and 300 mg/day doses. In this study, the major side effects associated with bupropion SR compared with placebo were insomnia and dry mouth. In accordance with these results, the 300 mg/day dose (150 mg b.i.d.) was recommended as the target dose for bupropion therapy for smoking cessation, with an initial dose of 150 mg/day for 3–4 days.

Several recent studies have extended the use of bupropion for smoking cessation. Hays et al. (160) examined the effects of bupropion versus placebo on the prevention of smoking relapse in 784 cigarette smokers who achieved smoking abstinence after a 7-week open-label trial of bupropion (300 mg/day). Those subjects who were abstinent from smoking at the end of the open-label phase of the trial (58.8%) were then randomized to receive bupropion (300 mg/day) or placebo for an additional 45 weeks. At the end of the 52-week treatment period, significantly more smokers in the bupropion group were abstinent than in the placebo group (55.1% vs. 42.3%; p<0.01) but not at the 1-year postmedication follow-up assessment (41.6% vs. 40.0%). The number of days to smoking relapse was higher in the bupropion than in the placebo group (156 vs. 65; p<0.05), and weight gain was significantly less in the bupropion group at the end of the 52-week treatment and at 1-year follow-up.

Dale et al. (1580) randomly assigned 615 subjects who smoked at least 15 cigarettes/day to placebo or to 100, 150, or 300 mg/day bupropion SR in a double-blind fashion. At the end of the 7 weeks of active treatment, bupropion SR showed improved rates of smoking abstinence in a dose-dependent manner.

It is not clear whether bupropion is superior to NRT or whether the addition of NRT to bupropion improves overall cessation rates. In one study, the combination of bupropion with the nicotine patch was evaluated in a double-blind, placebo-controlled, randomized, multicenter trial (159). The 893 cigarette smokers in that study, who smoked at least 15 cigarettes/day, were randomized to one of four experimental groups: 1) placebo bupropion (0 mg/day) plus placebo patch; 2) bupropion (300 mg/day) plus placebo patch; 3) placebo bupropion plus nicotine patch (21 mg/day for 4 weeks, with 2 weeks of 14 mg/day and 2 weeks of 7 mg/day); or 4) bupropion plus nicotine patch. Bupropion was administered 1 week before the target quit date (day 15), at which time patch treatment was initiated for a total of 8 weeks. All subjects received weekly individual smoking cessation counseling. Cessation rates at the 1-year follow-up assessment were 15.6% for placebo, 16.4% for active patch alone, 30.3% for bupropion alone, and 35.5% for the combination of nicotine patch and bupropion. The bupropion plus nicotine patch and bupropion alone conditions were significantly better than the placebo and nicotine patch alone conditions, but the combination (35.5%) was not significantly better than bupropion alone (30.3%). Weight suppression after cessation was most robust in the combination therapy group. Side effects were consistent with the profiles of patch and bupropion, and the combination was well tolerated. However, a higher-than-expected rate of treatment-emergent hypertension (4%–5%) was noted with the combination of bupropion and nicotine patch (159). The patch alone treatment was significantly different from placebo at the end of the trial but not at the follow-up assessments.

Other studies have suggested the efficacy of bupropion SR for smoking cessation in African Americans (670) and for smokers who have not responded to initial bupropion therapy (1583), smokers with chronic obstructive pulmonary disease (918) or cardiovascular disease (917), and users of smokeless tobacco (1584, 1585).

Finally, studies have suggested the utility of bupropion SR for smoking cessation/reduction in psychiatric and substance-abusing smokers. Using a secondary analysis of the Hurt et al. (158) study, Hayford et al. (1586) found that bupropion SR was equally efficacious for smoking cessation in individuals with or without a history of major depression or alcoholism. Similarly, Cox et al. (454), in a multicenter, randomized, double-blind relapse prevention trial of bupropion (300 mg/day) with 784 smokers, found bupropion to be effective regardless of whether patients had a history of depression or not. Finally, Chengappa et al. (458) found good rates of response to an open-label trial of bupropion for smoking cessation in 25 smokers with remitted major depression who were receiving maintenance SSRI, with 8 of the 25 (32%) subjects stopping smoking at the end of the 9-week trial. These findings suggest that bupropion's actions on nicotine dependence are independent of its antidepressant effects.

Bupropion SR has also been evaluated in three trials of patients with schizophrenia and nicotine dependence, including an open-label trial of 300 mg/day (415) and placebo-controlled trials of 150 (704) and 300 (414) mg/day. Weiner et al. (415) conducted a 26-week open-label trial of bupropion SR (300 mg/day), with 14 weeks of initial group CBT in eight patients with schizophrenia and nicotine dependence. Although none of the patients quit smoking during the trial, they did decrease their cigarette use, as indicated by an overall reduction (about 40%) in expired carbon monoxide levels at the end of the trial compared with pretrial levels. Of the four patients who chose to continue bupropion treatment for an additional 12 weeks after the trial, one stopped smoking completely, two had further decreases in expired carbon monoxide levels, and one maintained the decrease attained during the trial. In additional, negative symptoms of schizophrenia were reduced by bupropion during the trial, but this finding was not significant.

In a 12-week double-blind, placebo-controlled trial, Evins and colleagues (704) added bupropion SR or placebo to concurrent CBT for 18 patients with schizophrenia and nicotine dependence. Compared with placebo, treatment with bupropion led to an approximately 40%–50% reduction in carbon monoxide levels by the end of the trial. In addition, one of the nine subjects in the bupropion group versus none of the nine subjects in the placebo group achieved smoking cessation by the end of the trial. Both the positive and negative symptoms of schizophrenia were found to be reduced by bupropion during the trial.

In the third study, George et al. (414) conducted a 10-week double-blind, placebo-controlled trial of bupropion SR (300 mg/day) in 32 nicotine-dependent smokers with schizophrenia or schizoaffective disorder. All subjects received weekly group therapy emphasizing motivational enhancement, relapse prevention, and social skills training. Trial endpoint cessation rates (confirmed by a carbon monoxide level <10 ppm) were 50% (8 of 16) in the bupropion group and 12.5% (2 of 16) in the placebo group (p<0.05). Positive symptoms of schizophrenia were not affected, but negative symptom scores were reduced by about 15% in the bupropion group. In addition, treatment with a second- versus a first-generation antipsychotic medication strongly predicted success in smoking cessation in patients with schizophrenia.

The results from these preliminary placebo-controlled trials of bupropion suggest that smoking reduction and cessation are possible in patients with schizophrenia, exacerbation of psychotic symptoms is unlikely, and negative symptoms of schizophrenia may be reduced. With endpoint cessation rates of 11%–50%, bupropion may be more effective at higher doses (300 vs. 150 mg/day) in this population.

(3) Side effects

The primary side effects reported with bupropion administration in cigarette smokers are headache, nausea and vomiting, insomnia, and activation, most of which occur during the first week of treatment, although insomnia can persist (158, 159, 795, 1587–1590). Seizures are of exceedingly low occurrence (<0.5%) at doses of ≤300 mg/day, but a history of seizures or a seizure disorder would suggest a need for caution in prescribing bupropion (795, 1590). In addition, the use of bupropion is not recommended in individuals with a past or particularly a current diagnosis of an eating disorder because one study found an increased risk of generalized tonic-clonic (grand mal) seizures in bupropion-treated patients with bulimia (1591). The risk of hypertension with bupropion is <1% in smokers but may be higher in combination with an NRT (159).

(4) Implementation of bupropion therapy

For the treatment of nicotine dependence, the target dose of bupropion is 300 mg/day, taken in two doses of 150 mg each. Bupropion is started 7 days before the target quit date at 150 mg/day and, after 4–5 days, the dose is increased to 150 mg b.i.d. Currently there are few data as to which subgroups of smokers may benefit most for treatment with bupropion, although

smokers with depressive symptoms may benefit from the medication's antidepressant properties independent of its efficacy in treating nicotine dependence.

c) Nortriptyline

Nortriptyline is a TCA that has been shown to be superior to placebo for smoking cessation in randomized, double-blind, placebo-controlled trials (456, 795, 814, 815, 1592) and to have comparable efficacy to bupropion (795, 814, 1579). Some evidence suggests that its benefits persist for up to a year of treatment (895) and that its efficacy can be augmented by concomitant use of the nicotine patch (455); however, data on adding psychosocial therapies to nortriptyline treatment are mixed (456, 895, 1579).

Nortriptyline's mechanism of action in treating nicotine dependence is unclear, although the medication does block reuptake of norepinephrine and serotonin and may have indirect effects on dopamine (816). In addition, its mechanism in nicotine dependence may be distinct from its mechanism in treating depression, because its efficacy in smoking cessation is unrelated to the presence or absence of depressive symptoms or major depressive disorder (456, 795, 815, 816).

Side effects of nortriptyline are frequent (455, 815, 816) and include anticholinergic effects (e.g., dry mouth, blurred vision, constipation, tachycardia, and urinary hesitancy or retention), sedation, orthostatic hypotension, and cardiac conduction changes (817). The toxicity of nortriptyline in overdose amounts also needs to be taken into consideration when prescribing this medication. Nevertheless, nortriptyline appears to have some utility in smokers and can be recommended as a second-line agent after NRT and bupropion, although further study of this agent is necessary.

d) Clonidine

Clonidine is a presynaptic α_2-adrenergic agonist that dampens sympathetic activity originating at the locus coeruleus (602, 749, 1593). Because of its suggested efficacy for alcohol and opioid withdrawal, it was tried with nicotine withdrawal as well (749, 1593). Several clinical trials have used oral or transdermal clonidine in doses of 0.1–0.4 mg/day for 2–6 weeks with and without behavioral therapy; a meta-analysis of these trials suggested that clonidine is efficacious (818). In general, however, the effects of clonidine have not been as robust as the effects of NRTs or bupropion. The most common side effects of clonidine treatment are dry mouth, sedation, and constipation (818, 819, 1594). Postural hypotension, rebound hypertension, and depression are rare when clonidine is used for smoking cessation treatment (1594).

e) Other pharmacotherapies

A number of other pharmacotherapies for nicotine dependence have been studied, but there is insufficient evidence to support their use. Mecamylamine, an oral antihypertensive agent, is a noncompetitive ion channel blocker of high-affinity CNS and peripheral nicotinic receptors (820, 821, 1595) that decreases the positive subjective effects from cigarettes. In several small trials (820, 821), it was shown to result in an initial increase but a subsequent decrease in cigarette use. It has been postulated that naltrexone, the long-acting oral form of the short-acting intravenous opioid antagonist naloxone, would be useful in treating nicotine dependence because the performance-enhancing and other positive effects of nicotine may be opioid mediated (1596). Although one preliminary study showed benefits of naltrexone in combination with nicotine patch therapy (1597), naltrexone did not appear to decrease smoking in other studies (603, 822) and may even have increased smoking in some individuals (749, 1598). Buspirone, a 5-HT_{1A} receptor partial agonist anxiolytic agent, has been noted to improve short-term smoking cessation rates in a general population of smokers; it improved abstinence in high-anxiety smokers in one study (1599) but not in another (823, 1600). The alkaloid lobeline, which appears to have dopamine reuptake blockade and nicotinic receptor antagonist properties (1601), was evaluated in a 6-week, randomized, double-blind, placebo-controlled,

multicenter trial but did not produce any differences in smoking cessation rates (1602). Thus, there is little evidence that these diverse pharmacotherapies are useful for smoking cessation.

In addition to bupropion and nortriptyline, other antidepressive agents have been studied in nicotine-dependent patients. The available evidence gives little support for the use of SSRIs to assist in smoking cessation, either alone (1603, 1604) or in combination with NRT (1605, 1606). Although possible benefits have been found for the monoamine oxidase A inhibitor moclobemide (1607) and the monoamine oxidase B inhibitor selegiline hydrochloride (1608) for smoking cessation, larger trials of these agents are warranted. At the present time there is no evidence that other antidepressants are efficacious in treating nicotine dependence (795).

f) Somatic treatments

Acupuncture is often proposed for use in nicotine dependence, with the rationale that it may release endorphins that assist in smoking cessation. The efficacy of auricular acupuncture has been supported by some (786) but not other (1609) studies. The results of two more recent controlled studies (785, 1610) suggest that active versus sham acupuncture can lead to short- and long-term reduction in cigarette smoking but not smoking cessation. In addition, a meta-analysis of multiple other smaller studies of acupuncture has found no evidence for acupuncture efficacy in smoking cessation (788). In accordance with these results, acupuncture cannot be recommended as a treatment for smoking cessation.

Other somatic treatments that have been proposed include black pepper extracts (1611), capsaicin (1612), denicotinized tobacco (1613–1615), cigarette flavorings (1616), regenerated (denicotinized) smoke (1617), and citric acid inhaler (1618, 1619), all of which decrease cigarette craving or withdrawal symptoms or provide a substitute for the satisfaction from cigarettes in laboratory tests. However, none of these modalities have been sufficiently studied to recommend their use.

Cigarette filters have also been used to help smokers gradually reduce the amount of nicotine inhalation; however, studies of the efficacy of filters are inconclusive (1620, 1621), and smokers may to some extent adjust the frequency or depth of inhalation to compensate for such changes (1620, 1621). Thus, there is insufficient evidence to recommend filters as a treatment at this time.

2. Psychosocial treatments

a) Goals

The goals of psychosocial therapies for nicotine dependence include 1) providing individuals with the necessary skills to initiate abstinence, 2) teaching skills to avoid relapse to tobacco use in high-risk situations, 3) supporting and extending the effects of proven pharmacotherapies for nicotine dependence, and 4) facilitating a transition toward eventual smoking abstinence in smokers who are unable to quit immediately.

b) Efficacy

Psychosocial therapies appear to be effective treatments for nicotine dependence either alone or in combination with pharmacotherapies. The descriptive (827, 1580, 1622) and meta-analytic (720, 824–826, 828) reviews of psychosocial interventions for smoking cessation provide more information on efficacy.

c) Side effects

The side effects of psychosocial therapies for smoking cessation are considered minimal. Some factors should be taken into account when more intensive psychosocial therapies are considered, including their length and intensity. For these reasons, the majority (about 95%) of smokers do not desire or tolerate psychosocial therapies beyond minimal interventions.

d) Implementation

Although pharmacotherapy (bupropion or NRT) is recommended for all patients, a stepped-care approach in implementing psychosocial treatments for smoking cessation in general medical populations is recommended; thus, in initial smoking cessation attempts, social support and brief interventions (e.g., brief counseling, telephone support) should be tried first (826). If they are ineffective, more intensive behavioral treatments can be considered because there is a strong association between the intensity (826) and duration (895) of tobacco dependence counseling and its effectiveness. This strategy of a stepped-care approach to psychosocial treatment is supported by the fact that most smokers will continue to seek treatment despite repeated unsuccessful attempts at abstaining from smoking (1623, 1624).

Both group and individual formats of psychosocial therapies have been used for smoking cessation (720, 721, 742); groups can increase social support and individual treatment can address the particular problems of the smoker. In terms of the format of interventions, it is not clear whether individual or group psychosocial treatments are superior to one another; this may depend on the subtype of smoker and/or the treatment setting. Although studies of matching therapies to particular types of smokers have been published (1625, 1626), at present there are insufficient data to recommend specific matching strategies. Thus, patient preference should be considered when recommending group or individual treatment or when choosing a specific psychosocial treatment approach.

Because nearly 67% of patients relapse in the first week after a smoking cessation attempt (698, 794), most treatment is timed to occur over the few weeks immediately before and after the quit date (742). The most common providers of psychosocial therapies for smoking cessation are self-help groups (e.g., Nicotine Anonymous), state health departments, community organizations (e.g., American Cancer Society, American Lung Association), wellness programs, clinics for the treatment of substance use disorders, or health educators and psychologists in health care organizations (172). However, some treatments may not be available or be available only intermittently to patients, be costly, and not be integrated into the health care system. Consequently, many of those motivated to quit smoking forgo psychosocial therapy (172).

e. Specific techniques

The specific psychosocial interventions that have been evaluated for the treatment of nicotine dependence are described below.

(1) Social support

A number of studies have demonstrated the effectiveness of social supports (e.g., buddy systems, partner support) as treatments for smoking cessation (718, 826, 830–833). In some research, social support has been provided as an active intervention, whereas in other studies the supportiveness of a spouse or partner has been assessed independently without a specific intervention occurring (829). Interventions to enhance the degree of support provided by a spouse or partner have not produced significant differences in support levels and, not surprisingly, have not influenced smoking cessation rates (1627). Nevertheless, the effect of social support as an active intervention is significant, and it is thus recommended as a treatment for smoking cessation.

(2) Brief therapies

Several studies in controlled settings have documented that smoking cessation rates can be augmented by minimal behavioral interventions such as community support groups (845) and telephone counseling (846, 847). MET, which is often a component of brief interventions, encourages the smoker to weigh the reasons for and against quitting, thereby facilitating a choice of whether to quit or not. Several studies have suggested that brief interventions may be effective in promoting confidence in smoking cessation and treatment retention, even when cessa-

tion rates do not seem to be significantly improved (639, 834, 1628). In addition, training programs for physicians in basic behavioral counseling to support cessation may lead to enhanced cessation rates simply because physicians are more likely to engage patients in a discussion about smoking cessation (835). Such brief interventions also seem to have efficacy in promoting smoking cessation in hospitalized medical patients (836, 837), although this was not true across all studies (855). Thus, there is good evidence to recommend brief interventions in smokers making initial attempts at cessation and without prior unsuccessful treatment (826, 828).

(3) Behavioral therapies

Behavioral therapy is based on the theory that learning processes operate in the development, maintenance, and cessation of smoking. There have been >100 controlled prospective studies verifying the efficacy of behavioral therapy (720, 734, 735, 838). Behavioral therapies are typically a multimodal package of several specific treatments. In most reviews and meta-analyses, 6-month quit rates with behavioral therapy packages have been 20%–25%, and groups treated with behavioral therapy typically have had a twofold increase in quit rates as compared with control groups (718–720, 734, 735, 824, 825, 838, 1620). These cessation rates with behavioral therapy are similar to long-term outcomes obtained with medications such as NRTs and bupropion. Given this large database of efficacy, multimodal behavioral therapy is a recommended first-line treatment.

Several specific types of behavioral therapies have also been studied, but none are recommended at the present time. With contingency management, which has some evidence for short-term efficacy, behaviors consistent with smoking cessation are reinforced by giving a reward (e.g., money, vouchers) when patients are abstinent and denying them the same rewards if they are not (1629). However, once the contingencies are removed, smoking tends to return quickly. Thus, contingency management approaches might be best indicated in settings where a finite period of smoking abstinence is needed (e.g., during pregnancy, before surgical procedures). In addition, these techniques are probably best combined with CBT strategies.

Cue exposure involves repeatedly exposing patients to real or imagined situations that evoke potent urges to smoke to extinguish the ability of these situations to evoke these urges (1630–1633). Controlled studies (718), however, do not support the efficacy of cue exposure.

In aversion therapy, patients are asked to engage in "rapid smoking," in which inhaling cigarette smoke every few seconds produces a state of mild nicotine intoxication accompanied by nausea, dizziness, tremors, and other symptoms that will negatively reinforce smoking behavior (693, 734, 735). This technique has shown efficacy in many controlled studies, and most reviews and meta-analyses have concluded that rapid smoking is efficacious; however, the available studies have had methodological problems (1634) and adherence to the technique is low (718, 719, 734, 735, 741, 742, 838).

(4) Cognitive-behavioral therapies

For smokers who have failed initial treatments, the use of more specialized and higher-intensity behavioral treatments such as CBT in combination with NRT or bupropion is recommended. In CBT, patients anticipate situations where they are likely to smoke (e.g., at a party, during an argument) and plan strategies to cope with these situations without smoking. Behavioral coping includes removing oneself from the situation, substituting other behaviors (e.g., walking, exercising), or using skills (e.g., assertiveness, refusal skills, time management) to manage triggers. Cognitive coping includes identifying maladaptive thoughts, challenging them, and substituting more effective thought patterns (e.g., reminding oneself of why it is important to stop smoking or that the urge will pass) or trying to prevent a slip from becoming a relapse (e.g., not viewing the slip as a catastrophe). Some degree of efficacy of CBT has been demonstrated in smokers with a history of depression, alcohol dependence, and substance abuse (456, 459,

841–844). CBT has also demonstrated some degree of efficacy in addressing weight concerns associated with smoking cessation (840). However, differences in study design and control groups make comparisons of the studies difficult.

(5) Self-guided therapies

The major goals of self-help materials and procedures are to increase a smoker's motivation to quit and to teach smoking cessation skills. Most self-help materials are behaviorally oriented, and written manuals are the most common form of self-help material, although computer and video versions have also been developed (856, 859). In controlled settings, computer-generated tailored self-help materials (848, 849, 852, 853) can augment smoking cessation rates in those who adhere to the self-help program. Whether self-help interventions used without additional contact or support increase smoking cessation is debatable (720, 734, 735, 742, 838, 851, 859, 1451). Self-help materials appear to be more effective in patients who are less nicotine dependent (860, 1635) and more motivated (859). The use of multiple modes of therapy (e.g., written materials plus phone contact) appears to enhance the effectiveness of self-help (721, 856, 859). Tailoring materials to the specific needs and concerns of each patient also appears helpful (736, 851, 860). Telephone counseling in response to smokers' calls to a hot line appears to increase cessation when added to other self-help interventions (856–858), and meta-analyses suggest a small positive effect for such combined support (718, 720).

(6) Other therapies

A number of other therapies have been studied in small samples or used in clinical settings. One well-controlled randomized study provided evidence that exercise may assist with the prevention of smoking relapse and weight gain related to cessation (1636); however, another did not (863). In fact, a recent meta-analysis found that only 1 out of 11 studies examining the effects of exercise for smoking cessation had positive results; most of these studies were of small sample size and insufficient design (864). Nonetheless, it is recommended that exercise and increased activity be encouraged in smokers attempting to quit or who have recently quit smoking. Biofeedback, 12-step programs, family therapy, and psychodynamic therapies for the treatment of nicotine dependence have been minimally studied, and scientific evidence for their use is limited. Nevertheless, there is clinical consensus that such therapies may be useful in some patients.

Stimulus control is probably best used in the context of multicomponent therapies. It involves initially removing or avoiding cues associated with smoking to reduce urges to smoke. These strategies include discarding cigarettes; removing ashtrays, lighters, and matches; avoiding smokers; and avoiding situations associated with smoking. There is some support for the effectiveness of these techniques alone (718), but they require further study.

Physiological feedback, which presumes that abstinence will be reinforced by giving smokers immediate positive feedback about the decline in carbon monoxide levels when they stop smoking (718), has also been assessed. Although the rationale behind physiological feedback seems logical, actual findings are weak.

Gradual cessation procedures require smokers to gradually reduce the nicotine yield of their cigarettes by 1) increasing the time between cigarettes, 2) switching to cigarette brands with a lower nicotine content, or 3) using graduated filters ("faders") to progressively reduce the delivery of nicotine from the same brand of cigarettes (743, 1637). However, evidence for the efficacy of these treatments in improving quit rates is mixed, and meta-analyses have not supported their efficacy (718, 719).

Relaxation techniques are often taught to smokers to help them manage relapse situations that are associated with anxiety. Although often used in multicomponent programs, relaxation itself has not been shown to increase smoking cessation in most studies (734, 735, 741, 742, 1620) or in a meta-analysis (718). There is also little scientific validation for the effectiveness

of hypnotherapies for smoking cessation, despite the fact that they are commonly used by individuals who wish to stop smoking.

▶ B. ALCOHOL-RELATED DISORDERS

1. Treatment settings

Studies of specific settings for the treatment of alcohol-related disorders have been relatively limited. Such studies may also be subject to selection bias in terms of the characteristics of patients willing to be randomized to different treatment settings (1638).

Most (52, 1639–1641) but not all (1303) studies that have randomly assigned patients to different levels of treatment have not found an advantage for inpatient care over less restrictive settings. However, for safety reasons, these studies have been required to exclude from randomization individuals who would ordinarily be considered to require inpatient treatment (1642). For example, the study by Hayashida et al. (48) randomly assigned alcohol-dependent patients coming to a VA hospital to inpatient or outpatient detoxification but excluded those who required hospitalization for medical reasons. However, those excluded were only 10% of the population applying to this clinic. Another study among male veterans (1643) showed that the mortality rates for individuals with an alcohol use disorder 3 years after discharge varied with the initial treatment setting. Veterans who completed inpatient rehabilitation had the lowest mortality rate, whereas those in the following groups had an increasingly high mortality rate, respectively: 1) those who had at least 6 days of inpatient treatment (but did not complete the program), 2) those who were admitted for brief detoxification lasting <5 days, and 3) those who received no specific treatment for their alcohol use disorder. This study provided preliminary evidence that more intensive treatment may lower the mortality associated with a chronic alcohol use disorder. However, patients in this study were not randomly assigned to treatment conditions, so it is possible that self-selection influenced the results.

Some evidence suggests that longer treatment stays and treatment completion may be associated with better outcomes (959, 1304). This probably reflects the fact that more motivated patients are more likely to stay in treatment and have better outcomes, because differences in outcome are not typically observed when patients are randomly assigned to shorter versus longer treatments (51, 956).

Other evidence suggests that the association between treatment setting and outcome may be a complex one that is influenced by the characteristics and treatment needs of the individual patient. Magura et al. (965) studied a cohort of 248 patients who were newly admitted to inpatient rehabilitation or intensive or regular outpatient care and determined whether they were naturalistically matched or mismatched to care according to ASAM patient placement criteria. At 3 months after intake, individuals who received regular outpatient care when intensive outpatient care would have been recommended as more appropriate had poorer drinking outcomes. In individuals who received residential as compared with intensive outpatient treatment, there also was a trend for a better outcome. Rychtarik et al. (966) also examined individual factors that might determine the appropriateness of a given treatment setting for an individual patient. They found that individuals with a high level of involvement with alcohol and lower cognitive abilities had better outcomes when treated in inpatient settings, whereas those with lower levels of alcohol involvement did better in outpatient settings.

2. Pharmacological treatments for withdrawal

Benzodiazepines are effective in treating alcohol withdrawal symptoms, particularly when compared with placebo in the prevention of withdrawal seizures (991, 992, 995). In preventing sei-

zures, benzodiazepines appear comparable in efficacy to anticonvulsants, although the significant heterogeneity of relevant clinical trials makes comparisons difficult (995). Nevertheless, meta-analyses have consistently demonstrated the benefits of benzodiazepines in treating alcohol withdrawal. One meta-analysis (992) examined 134 studies, including 65 prospective controlled trials involving 42 different medications. This analysis concluded that benzodiazepines reduce withdrawal severity and the incidence of seizures and delirium (992). Another meta-analysis of 11 randomized, controlled trials found benzodiazepines to be superior to placebo, with no study demonstrating that any other class of agent, including beta-blockers, carbamazepine, and clonidine, was more beneficial than benzodiazepines (991). Most recently, Ntais et al. (995) analyzed 57 trials that included a total of 4,051 people and concluded that benzodiazepines are effective against alcohol withdrawal symptoms when compared with placebo.

Evidence from multiple randomized, controlled trials also supports the use of symptom-triggered therapy, with symptom-triggered detoxification protocols leading to less use of medication as well as shorter duration of treatment than fixed-dose protocols (998, 1001–1003). An additional clinical trial of outpatient detoxification using chlordiazepoxide prescribed according to a symptom-triggered detoxification protocol showed that, on average, patients received 167 mg of the medication over 2.7 days and 85% completed the protocol (1644); however, this study did not use a randomized, placebo-controlled design.

One randomized, double-blind, placebo-controlled study compared lorazepam with placebo for the prevention of recurrent seizures related to alcohol withdrawal (1005). This study found that treatment with intravenous lorazepam was associated with a significant reduction in the risk of recurrent seizures related to alcohol.

One meta-analysis (992) considered four randomized, controlled trials of carbamazepine and concluded that carbamazepine was superior to placebo and equal in efficacy to phenobarbital and oxazepam for patients with mild to moderate withdrawal. Another study compared the efficacy of carbamazepine and lorazepam for detoxification in patients with more than one previous detoxification for alcohol withdrawal compared with those with one or no previous alcohol withdrawals (977, 1019). The authors found that healthy middle-age male outpatients randomized to carbamazepine or lorazepam had comparable outcomes in terms of symptoms of alcohol withdrawal. However, carbamazepine was superior to lorazepam in preventing rebound withdrawal symptoms and reducing posttreatment drinking, especially among those with multiple past detoxifications (977).

With respect to the use of other anticonvulsants for detoxification, one recent review concluded that there is no current evidence that divalproex sodium is effective in treating alcohol withdrawal (987), but one study demonstrated that divalproex sodium used as adjunctive pharmacotherapy with oxazepam reduced the total amount of oxazepam needed for detoxification (994). There have been two other open-label trials of divalproex to treat alcohol withdrawal: one compared divalproex with lorazepam in 11 patients and concluded that divalproex ameliorated alcohol withdrawal symptoms and decreased the amount of lorazepam needed for detoxification (1020), and another found that valproate was as effective as phenobarbital in managing acute withdrawal (1018).

Studies of adrenergic agents have been quite small, limiting the generalizability of their conclusions. For example, one randomized, controlled trial of 37 male patients admitted for uncomplicated detoxification compared diazepam 10 mg p.o. with propranolol 20 mg p.o., repeating the medication dose every 4 hours for continued withdrawal symptoms (1645). The patients randomized to diazepam or propranolol showed improvements in blood pressure level, pulse rate, and withdrawal tremors. However, one subject in the propranolol group had a withdrawal seizure, whereas no subject randomized to diazepam manifested a withdrawal seizure or hallucinations. Another study compared intravenous diazepam, clonidine, and alprazolam treatment of alcohol withdrawal and found diazepam was more effective than clonidine and placebo for some measures of withdrawal (1646).

3. Pharmacological treatments for dependence and abuse

a) Naltrexone

(1) Goals

The goals of pharmacotherapy for alcohol dependence can be multifaceted. Medications may help maintain or improve abstinence, reduce heavy alcohol consumption, decrease relapse rates to heavy drinking, or more generically reduce craving, an intermediary step to the above clinical goals.

(2) Efficacy

It is thought that alcohol exerts its rewarding, euphoric, and subsequent craving effects, at least in part, by stimulating opiate receptors. Naltrexone, an opiate receptor antagonist, blocks this effect. Alternatively, opiate receptor antagonism may play a role in diminishing the rewarding aspects of alcohol-induced dopamine release. Naltrexone is one of the most widely studied medications for the treatment of alcohol dependence, with randomized, controlled clinical trials having been performed not only in the United States but also in many European countries and Australia. Most published studies have evaluated naltrexone against placebo for its ability to promote abstinence, reduce heavy drinking days, and decrease rates of relapse. Enough data from randomized, controlled trials have been published to allow for several meta-analyses (e.g., references 152, 153). These meta-analyses concluded that naltrexone was more efficacious than placebo across most of the drinking outcome variables referred to above.

This advantage of naltrexone is small to moderate, with effect sizes of 0.1–0.5 and/or relative risk decreases of 10%–14% depending on the drinking measure. It also appears from research studies and clinical experience that some patients respond to naltrexone and others do not. It has been suggested that a family history of alcoholism, genetic differences in opiate alleles (1647), and high levels of craving may be predictive of naltrexone response. However, when evaluating published studies on naltrexone, there are two significant issues to consider: patient adherence to treatment and the concomitant psychosocial intervention used.

The role of medication adherence was emphasized by Pettinati et al. (1648) in their reanalysis of data from several clinical trials completed at their site. In that review, they observed a marked difference in naltrexone response between patients who adhered to the medication regimen and those who did not. This finding has led others to evaluate the factors that predict adherence to naltrexone treatment among alcohol-dependent subjects (1513). These authors and others (1649) have suggested that high levels of side effects during the first several weeks of treatment reduces adherence and that higher craving levels at study entry, as well as a greater belief in naltrexone's efficacy, may predict better medication adherence. Day-to-day fluctuations in patient motivation to take naltrexone may be overcome through the use of a long-acting injectable form of the medication. This formulation has been designed to release a small amount of naltrexone in the first few days (1650) and has been shown to have good tolerability in a multisite study (24 sites with 624 subjects) without dose titration or initial oral naltrexone (1044).

Several studies (187, 1039) have indicated that naltrexone works best when combined with a relapse prevention (coping skills, CBT) approach. This observation is supported by other studies (1038, 1041). In general, when naltrexone was given to more severely alcohol-dependent subjects without a concomitant defined relapse prevention intervention, its efficacy was less robust (1045) or nonexistent (1043).

The FDA approved naltrexone for use in treating alcohol dependence in 1994 based on several small single-site studies (187, 1037). Although the results from a number of single-site and small multisite studies from several countries have supported the utility of naltrexone (954, 1038–1041) in intent-to-treat analyses, those from a few larger multisite studies have been negative (1042, 1043). In one multisite randomized, controlled trial (1043), 627 predominantly male alcohol-dependent veterans were treated for up to 52 weeks with 50 mg naltrexone or pla-

cebo. Participants also received TSF and other treatment "as usual." The results showed that compared with placebo, naltrexone had no effect on abstinence rates, number of days to relapse, percentage of drinking days, or number of drinks per drinking day. In this trial there were several differences compared with other naltrexone studies that had positive results; the most significant of these were 1) the subjects were older and more severely affected by alcohol, 2) the background psychosocial intervention (TSF) may have been more varied, 3) the dropout rate was slightly higher, and 4) there was more variability inherent in this multisite study when compared with single-site studies.

In a 12-week German multisite study (1042), 171 "detoxified" alcoholic subjects from seven centers were treated with 50 mg/day naltrexone and at least 1 hour a week of psychosocial intervention "as usual." There was no statistical difference between naltrexone and placebo on time to first heavy drinking episode, time to first drink, or overall alcohol consumption or craving. However, the naltrexone group had a statistically significant reduction in γ-glutamyl transpeptidase (a liver enzyme measured in blood that serves as a marker of heavy alcohol consumption) compared with placebo. These study results need to be interpreted cautiously, however, because 1) the average participant was abstinent for almost 20 days before starting naltrexone and the relapse rate overall was lower than that in most other studies, 2) the psychosocial treatment was not standardized, and 3) the dropout rate was relatively high (33%–38%).

(3) Side effects

Naltrexone's side effects have generally been moderate at the 50-mg dose used in most studies, and have included gastrointestinal problems (nausea, vomiting, abdominal pain) and CNS-related symptoms (headache, fatigue). The U.S. product label (as described in the *Physicians' Desk Reference*) warns that significant hepatoxicity may occur with naltrexone. This complication has been observed mostly in morbidly obese subjects receiving higher doses of naltrexone, whereas many clinical trials, including a safety study conducted for FDA review (1046), did not observe significant hepatoxicity. However, a more recent report (1047) describing an interaction between NSAIDs and high-dose naltrexone (>100 mg/day) that leads to hepatoxicity should be noted. Although the exact risk of this interaction is unknown, clinicians should use high doses of naltrexone cautiously and warn their patients of this potentially dangerous medication interaction.

(4) Implementation issues

To minimize any potential interaction of side effects caused by naltrexone and those normally occurring during alcohol withdrawal, a few days of alcohol abstinence should be achieved before naltrexone is initiated. In general, naltrexone is begun at 25 mg/day for a few days, followed by an increase in the dose to 50 mg/day, as tolerated. A gradual dose increase might reduce the gastrointestinal side effects that occasionally emerge early in treatment and generally moderate over time. Women might be more sensitive to the gastrointestinal effects of naltrexone and could be especially aided by a slower titration. At this time, there is no strong evidence that naltrexone doses of >50 mg/day are more efficacious, but some individual cases of greater efficacy at higher doses have been noted. Clearly explaining to patients the potential mild adverse effects of naltrexone and the tendency of these effects to improve over time and providing motivational enhancement to promote patient adherence to medication and alcohol reduction/abstinence may all lead to improved patient cooperation with medication and psychosocial treatments. Although it is not clear how specific psychosocial interventions interact with naltrexone, there is good evidence that relapse prevention therapies (e.g., CBT, coping skills) may allow naltrexone to have its maximal effect.

Because naltrexone is an opiate antagonist, individuals abusing opiates may experience opiate withdrawal when treatment is initiated, and those taking opiates for analgesic effects will find them ineffective during naltrexone treatment. Therefore, a complete medication history

and urine toxicology screen for opiate medication may be indicated before naltrexone therapy is initiated. In addition, caution should be taken if acute opiate analgesia is required during the course of treatment. For example, higher doses of opiates may be required, in which case the signs of respiratory distress should be monitored and treated appropriately. The naltrexone-treated patient should carry a card explaining these issues and provide it to health care personnel in an emergency.

b) Disulfiram

(1) Goals
The goal of treatment with disulfiram is to enhance the motivation of abstinent alcoholic individuals to resist alcohol consumption. Pretreatment with disulfiram establishes the conditions in which the subsequent use of alcohol will result in a toxic and highly aversive reaction. In theory, this knowledge should improve the patient's cognitive control over any urge to drink.

(2) Efficacy
Disulfiram inhibits the activity of aldehyde dehydrogenase, the enzyme that metabolizes acetaldehyde, a major metabolite of alcohol. The usual therapeutic dose is 250 mg/day, although some patients achieve optimal benefit at either a higher or a lower dose (range 125–500 mg/day). In the presence of disulfiram, alcohol consumption results in the accumulation of toxic levels of acetaldehyde, which in turn produces a host of unpleasant signs and symptoms including a sensation of heat in the face and neck, headache, flushing, nausea, vomiting, hypotension, and anxiety. Chest pain, seizures, liver dysfunction, respiratory depression, cardiac arrhythmias, myocardial infarction, and death have also been reported.

Controlled trials have not demonstrated any advantage of disulfiram over placebo in achieving total abstinence, delaying relapse, or improving employment status or social stability (1048, 1049). However, some clinicians believe that this medication, when combined with other therapeutic interventions, has benefit for some individuals who remain employed and socially stable (150, 1048, 1050–1052). Treatment effectiveness is enhanced when adherence is encouraged through frequent behavioral monitoring (e.g., breath tests), group support for remaining abstinent (e.g., group therapy, AA) (1053), contingency contracting, or, where feasible, supervised administration of disulfiram. Patients who are intelligent, motivated, and not impulsive and whose drinking is often triggered by unanticipated internal or external cues that increase alcohol craving are the best candidates for disulfiram treatment. Poor candidates might include patients who are impulsive, have poor judgment, or have a co-occurring psychiatric disorder (e.g., schizophrenia) that is severe enough to make the patient unreliable or self-destructive (149, 1060). However, some patients with schizophrenia might be able to use disulfiram correctly while under active maintenance with antipsychotics (363).

(3) Side effects
Disulfiram can cause a variety of adverse effects; hepatotoxicity and neuropathies with use of this medication are rare but potentially severe. In patients with moderate to severe hepatic dysfunction, peripheral neuropathies, pregnancy, renal failure, or cardiac disease, disulfiram should be used cautiously and potential benefits and risks for the individual patient should be considered (1048). Because one of the metabolites of disulfiram inhibits dopamine beta-hydroxylase, resulting in increased levels of dopamine, there is a theoretical risk of augmenting psychotic symptoms (409, 410). Thus, patients with a psychotic disorder should be observed for evidence of a worsening psychosis if treated with disulfiram.

(4) Implementation issues
Understanding and explaining disulfiram's toxic or lethal effects to patients are a prerequisite for its use (1056–1058), so it should never be used without the patient's knowledge and con-

sent. Patients taking disulfiram must be advised to avoid all forms of ethanol (including, for example, that found in cough syrup). In addition, disulfiram interferes with the metabolism of many medications, including TCAs, so that care must be taken to avoid toxicity (1651).

c) Acamprosate

(1) Goals
The goal of using a medication like acamprosate is to decrease the relapse rate to any drinking after an initial abstinence period has been achieved. It may work best in combination with a psychosocial intervention that promotes and facilitates abstinence.

(2) Efficacy
In 2004, the FDA approved acamprosate for the treatment of alcohol dependence, primarily based on data derived from European studies (reviewed in references 1062, 1063). Although the neuropharmacological action of acamprosate is not completely known, it is an amino acid derivative of taurine that is thought to work at brain glutamate receptor sites. In general, it is thought to stabilize glutamatergic function (155). As such, it has been hypothesized that it normalizes an aberrant glutamate system present during early abstinence that might be the basis of protracted withdrawal and craving during that period (1064).

European studies evaluating patients who generally started on acamprosate while in a hospitalized setting and were abstinent for at least 7–10 days have shown that with acamprosate treatment, there is an increase in the number of patients who maintain abstinence. Those who relapse have more abstinent time before their first drinking day and also more overall abstinent days during a year or more of treatment (1062, 1063). In contrast, a multisite trial completed in the United States did not find acamprosate to be effective in a primary intent-to-treat analysis, but it did find that when subjects' motivation to maintain abstinence and adhere to medication was taken into account, acamprosate was more effective than placebo in increasing the number of abstinent days (1067). The U.S. trial included outpatients who had a varied number of abstinent days before medication initiation, but, in general, overall pretreatment abstinent time was much shorter than that in the European trials. Also, in the U.S. trial, subjects received standardized medical management counseling, whereas in the European studies (1062, 1063) traditional psychosocial alcohol treatment approaches focusing on the maintenance of abstinence were generally used. It would appear that acamprosate is most effective in patients who have achieved a number of days (perhaps ≥7) of abstinence before starting the medication, although this theory has not been specifically studied.

(3) Side effects
Acamprosate at the FDA-approved dosage of two 333-mg pills three times each day (total dose 1998 mg) is well tolerated, with generally self-limiting and symptomatically treated diarrhea being the main adverse effect. Liver disease should not affect its metabolism or blood levels. Because acamprosate has minimal if any negative interaction with alcohol, it is expected to be generally safe in active or relapsed drinkers.

(4) Implementation issues
It is not clear if certain subgroups of alcohol-dependent individuals will benefit from acamprosate more than others. Data from European studies and a U.S. multisite trial suggest that some days of abstinence prior to initiation of acamprosate treatment might improve efficacy. In addition, a patient's strong motivation to maintain or achieve abstinence might also improve treatment response. Acamprosate can be started at a full dose immediately. It is generally taken three times per day to maintain blood levels and avoid unnecessary gastrointestinal problems. It should be well tolerated in individuals with compromised liver function because it is metabolized and excreted primarily through the kidneys. Individuals with renal impairment should

be monitored carefully when taking the medication; depending on the severity of the impairment, acamprosate might need to be avoided.

Data suggest it is safe to take acamprosate with naltrexone or disulfiram, and there are no known significant medication interactions.

d) Medications acting on the serotonin system

(1) Goals

The use of SSRIs in the treatment of alcoholism may have two distinct goals: 1) reduce drinking or promote abstinence through these medications' effect on the serotonin system, which is hypothesized to directly effect alcohol consumption (see discussion below); and 2) treat psychiatric syndromes/symptoms in alcoholic patients through the well-documented antidepressant and antianxiety effects of these agents. To the extent that anxiety and depression underlie drinking behavior, SSRI amelioration of these symptoms should lead to reduced drinking, a reduction of relapse, and the maintenance of abstinence. The selective $5\text{-}HT_3$ antagonist ondansetron is thought to have effects on alcohol reward and thereby reduce alcohol consumption and promote abstinence.

(2) Efficacy

There is considerable evidence that serotonin modulates the behavioral effects of alcohol (479, 1073–1075). SSRIs augment brain serotonergic function and have been shown to reduce alcohol consumption in animals. Medications in this class include fluoxetine, sertraline, paroxetine, and citalopram.

Several randomized, double-blind, placebo-controlled human studies with nondepressed heavy drinkers found SSRIs reduce alcohol consumption by 15%–20% in the short term (4–6 weeks) (1076, 1077). The results of these initial studies suggested that these medications could have an effect in reducing alcohol consumption. However, the results could not be easily generalized to the more severely impaired alcohol-dependent person. Indeed, results of trials using SSRIs to treat patients diagnosed with alcohol dependence have been less consistent (1078). A double-blind study comparing fluoxetine treatment with placebo in which both groups received CBT found no overall difference in drinking between groups (1079). However, further analysis showed that type B alcoholic individuals, characterized by early onset of drinking, heavier alcohol dependence, and greater co-occurring psychopathology, showed less favorable drinking outcomes in response to treatment with fluoxetine than with placebo. In contrast, the type A alcoholic individuals, characterized by later onset of drinking, less severity of dependence, and less psychopathology, did appear to benefit from fluoxetine. These findings were confirmed in a 14-week placebo-controlled trial of sertraline (200 mg/day) in alcohol-dependent patients stratified by subtype (1080). At this time, the treatment of nondepressed alcoholic patients with SSRIs remains controversial and may worsen drinking behaviors in some individuals.

Based on animal studies (1082, 1083) and early clinical laboratory findings (1084), the $5\text{-}HT_3$ receptor antagonist ondansetron was thought to have promise as a therapeutic agent in alcohol dependence, which led to its clinical evaluation. In a placebo-controlled outpatient trial with 71 mildly alcohol-dependent male subjects, a low dose (0.25 mg b.i.d.) but not a high dose (2.0 mg b.i.d.) of ondansetron moderately reduced alcohol consumption (1085). Using relatively low doses of ondansetron (2–32 μg/kg per day), Johnson et al. (1086) conducted a 12-week placebo-controlled clinical trial in 271 alcohol-dependent patients who also received weekly CBT. Patients with early-onset alcoholism who received ondansetron showed significant reductions in drinking (especially in the 4 μg/kg b.i.d. group) compared with those who received placebo. Patients with late-onset alcoholism had higher levels of drinking across all groups but showed no significant differences between medication and placebo treatment. The efficacy of ondansetron

in the treatment of alcohol dependence in patients with early-onset alcoholism has been documented in only this single-site placebo-controlled study (1086) and in an open-label study in which the same dose of ondansetron was used (1652). Replication studies have yet to be conducted, and ondansetron has not been approved by the FDA for alcoholism treatment.

(3) Side effects

SSRIs are generally well-tolerated medications and have many patient-years of use worldwide. They appear to have a good safety profile in heavy alcohol consumers. However, some side effects of these medications clearly overlap with alcohol-related effects. The most frequent side effects of SSRIs occur in the gastrointestinal tract (nausea, diarrhea), which is also affected by alcohol, both during withdrawal and during active drinking. SSRIs have effects on the CNS (activation/sedation and headache) that also may occur during alcohol withdrawal and active drinking. Perhaps the most difficult side effects to evaluate in the alcoholic patient are potential SSRI-induced changes in libido and sexual performance. These complaints may occur during changes in alcohol consumption under normal conditions, and the differential role of SSRIs may be particularly hard to evaluate.

Ondansetron may cause some gastrointestinal disturbances, headache, and fatigue. It has been generally well tolerated at the low doses used in alcoholism trials to date.

(4) Implementation issues

Because there is an overlap of signs and symptoms of alcohol withdrawal and SSRI side effects, a few days of abstinence from alcohol and monitoring of amelioration of alcohol withdrawal effects should occur before initiating an SSRI. A more gradual titration might minimize any interaction of alcohol-related and SSRI effects.

Awareness and documentation of individual differences in sleep at baseline, which may or may not be alcohol related (334), will assist the clinician in evaluating the potential SSRI effect on sleep during treatment. For example, many alcoholic individuals drink to be able to get to sleep, so if an SSRI is causing nocturnal activation, this may not only reduce its effectiveness for alcohol treatment but also may be a reason to avoid its use. If an SSRI causes sedation during the day, this effect may be augmented by alcohol if an individual relapses.

Because SSRI-related sexual complaints overlap with alcohol-related effects, a good medical and longitudinal history of these complaints is likely to be helpful. Documentation of these issues before initiating SSRI treatment should also assist the clinician in assessing these complaints should they arise during treatment.

If ondansetron is to be prescribed, the clinician and patient must be reminded that the doses used in the published clinical trials have been an order of magnitude lower than what is generally prescribed for the treatment of nausea. Ondansetron is currently available in pill form but at a higher dose strength than that found to be efficacious in early-onset alcoholic patients. It is also available in liquid form. In either case, care must be taken to provide the correct dosing.

4. Psychosocial treatments

a) Cognitive-behavioral and relapse prevention therapies

There is abundant evidence that CBT approaches aimed at improving a patient's self-control and social skills consistently lead to reduced drinking (79, 1090, 1092–1094). Subtypes of CBT strategies have been supported with generally positive but variable degrees of success. Cognitive therapy interventions that focus on identifying and modifying maladaptive thoughts but that do not include a behavioral component have not been as effective as cognitive-behavioral treatments (1090) and were found to be effective in only 4 out of 10 studies reviewed by Miller and Wilbourne (79).

Behavioral self-control training consists of cognitive and behavioral strategies, including self-monitoring, goal setting, rewards for goal attainment, functional analysis of drinking situations, and the learning of alternative coping skills (1095, 1096). Holder et al. (1090) and Hodgeson (1097) both found that cognitive-behavioral stress management interventions were effective in the majority of studies reviewed. Although some studies of behavioral self-control training have included controlled drinking as well as abstinence as a goal for treatment, behavioral self-control techniques should be with the explicit long-term goal of abstinence.

General self-control strategies include goal setting, self-monitoring, functional analysis of drinking antecedents, and learning alternative coping skills. Miller and Wilbourne (79) found that self-control training produced better outcomes than control treatments in 17 of 35 studies.

In several studies, increases in coping responses or "self-efficacy" (1098) at the end of treatment predicted better drinking outcomes during follow-up (184, 1099, 1100). Individuals who report more frequent use of cognitive or behavioral strategies aimed at problem solving or mastery ("approach coping") typically have better drinking outcomes than those who rely on staying away from high-risk situations ("avoidant coping") (959, 1101).

Outcome studies have typically supported the efficacy of group behavioral and CBT treatments, including group marital therapy. The results of studies matching patients to treatment in which patients were randomly assigned to cognitive-behaviorally oriented treatment groups or interactional therapy groups suggest that patients with fewer antisocial personality features or with neurological impairment fare better in interactional therapy; those with higher levels of antisocial personality features and psychopathology fare better in CBT groups (1102, 1103). Litt et al. (1104), in a randomized, controlled study, also found a positive effect of matching patients to treatment strategy.

(1) Relapse prevention strategies

In a meta-analysis of relapse prevention therapies, Irvin et al. (1094) found an effect size of 0.27 for treatment of alcohol use derived from five studies.

(2) Motivational enhancement therapy

MET and motivational interviewing, brief treatments aimed at maximizing the patient's intrinsic desire to change, were found to be efficacious in 7 of 9 studies reviewed by Dunn et al. (1105) and 12 of 17 studies reviewed by Miller and Wilbourne (79). This type of treatment is typically brief, lasting 1–4 sessions, and has been frequently used to enhance adherence with more intensive or extensive subsequent treatments. The use of MET as a stand-alone treatment was most notably supported by Project MATCH (43), in which 4 sessions of MET yielded equivalent results to 12 sessions of CBT or 12 sessions of TSF as an initial treatment or care after hospitalization. Alcohol-dependent patients in all three treatments experienced substantial and enduring improvement in drinking outcomes (43, 265).

b) Behavioral therapies

Individual behavioral therapy has been found to be effective for patients with an alcohol use disorder (191, 956, 1090), particularly those treatments that emphasize positive reinforcements for targeted behaviors. Behavioral contracting was found to be effective in four of five studies reviewed by Miller and Wilbourne (79). In contrast, relaxation training, a behavioral treatment that has been widely studied, was found to be ineffective in 17 of 18 controlled trials (79).

(1) Community reinforcement

The most comprehensive behavioral approach to the treatment of patients with alcohol use disorders is the community reinforcement approach, which uses behavioral principles and usually includes conjoint therapy, training in finding a job, counseling focused on alcohol-free social and recreational activities, monitoring of disulfiram use, and an alcohol-free social club (1107).

Using random assignment to community reinforcement treatment or standard hospital treatments, Azrin (190) found that patients in the community reinforcement group drank less, spent fewer days away from home, worked more days, and were institutionalized less over a 24-month follow-up period. A second controlled study comparing 1) the community reinforcement approach, 2) disulfiram plus a behavioral adherence program, and 3) regular outpatient treatment showed that patients treated with community reinforcement did substantially better on all outcome measures than those in the other treatment conditions (190). A meta-analytic review conducted by O'Farrell and Fals-Stewart (690) documented a medium effect size for the community reinforcement approach combined with marital therapy.

(2) Aversion therapy
Compared with positive reward approaches, aversion therapies have been less successful. Only a small number of studies (12 of 28) have documented the efficacy for aversion therapy using nausea or electric shock (79).

c)   Social skills training
Social skills training focuses on learning skills for forming and maintaining interpersonal relationships, being assertive, and refusing alcohol. Miller and Wilbourne (79) found social skills training to be effective in 17 out of 25 studies.

d)   Psychodynamic and interpersonal therapies
Holder et al. (1090) concluded that there was little empirical evidence from controlled studies that insight-oriented psychotherapy or counseling is an effective treatment for an alcohol use disorder. Individual psychotherapy produced better outcomes than a control condition in 2 of 8 studies reviewed, and psychodynamically oriented group psychotherapy produced better outcomes in 2 of 11 studies. Empirical research on the efficacy of psychodynamic treatment for substance abuse is limited by the long-term nature of this approach and difficulties in developing representative training manuals. However, there is a large body of clinical literature documenting success in individual patients in uncontrolled conditions (1653). A more recent review found support for individual therapy in 11 of 18 trials reviewed, although the quality of the studies was noted to be generally poor (79).

e)   Self-help groups and 12-step-oriented treatments
The effectiveness of AA, per se, has not been evaluated in randomized studies because of a host of ethical and practical problems associated with assigning patients to a group that does not attend AA (261). However, there is growing support for the utility of AA and 12-step-oriented treatments from a range of sources (reviewed by McCrady and Irvine [1115]). Several naturalistic studies have suggested that AA can be an important support for promoting an alcohol-free lifestyle in patients who are willing to attend (956, 958, 959). A large number of studies have documented that more AA participation is linked to better drinking outcomes (260–266, 289, 1113, 1114). For example, in an evaluation of 8,087 patients in 57 programs, Hoffman and Miller (1112) reported that those attending AA at 1-year follow-up were 50% more likely to be abstinent than those not attending AA.

Professional therapies based on AA have been also found to be effective (1115). Moos and colleagues (260, 262–264, 266), in a series evaluating outcome in alcoholic veterans treated in a 12-step or CBT-oriented program, documented overall better outcome for 12-step treatments and a strong association between AA involvement and improved outcome. The findings of Project MATCH were generally positive for TSF, an individual-based, professionally delivered psychotherapy aimed at motivating patients to adhere to AA principles. Compared with MET and CBT, main effects for drinking outcomes were comparable or modestly superior for TSF (43, 265), and selected significant matching effects favored TSF for patients who had low

severity of psychiatric symptoms, rated high on seeking meaning of life, and had high social support for not drinking.

Regarding patient-program matching, evidence from small-scale trials has suggested that patients with more severe drinking problems, an affective rather than a cognitive focus, a concern about purpose and meaning in life, better interpersonal skills, and a high need for affiliation are good candidates for AA (1115, 1654). In the landmark study Project MATCH, aftercare patients who rated high in the seeking meaning category fared better with TSF compared with MET and CBT at 1-year follow-up. Also, TSF was more effective than CBT for outpatients who did not show psychiatric symptoms and comparably equivalent for those with symptoms. Patients with high social support for not drinking had better drinking outcomes over the 3-year posttreatment period if they were treated with TSF rather than MET (1- and 3-year reports) (43, 265).

f) Brief interventions

Brief interventions generally delivered over one to three sessions include an abbreviated assessment of drinking severity and related problems and the provision of motivational feedback and advice. Brief therapies have typically been studied in general medical settings or school-based settings and have focused on non-treatment-seeking heavy drinkers who do not meet criteria for alcohol abuse or dependence. In 22 of 31 controlled treatment trials reviewed by Miller and Wilbourne (79), brief interventions were found to be effective. Reviews by Babor (1109) and Bien et al. (275) concluded that brief interventions 1) are typically more effective (in terms of alcohol use, general health, or social functioning) than no intervention; 2) often have efficacy comparable with that of traditional, more intense, longer-term programs; and 3) increase the effectiveness of later treatment. Even interventions that are very brief (i.e., a few hours) may have some positive effect (1110). For example, Fleming et al. (1111) conducted a trial of a brief physician advice condition plus a general health booklet versus the general health booklet alone in 774 primary care patients who screened positive for an alcohol use problem. This sample comprised 4.4% of 17,795 general medical patients screened. At 12-month follow-up, two 15–20-minute sessions of physician advice yielded significantly greater improvements in the number of alcoholic drinks taken over 7 days, the 30-day rate of binge drinking, and the rate of excessive drinking. Further research is needed to determine which patients are optimally served by receiving a brief intervention.

g) Marital and family therapy

The state of the patient's relationship with family members or significant others can be a critical factor in the posttreatment environment for patients who are married, in a committed relationship, or living with family members (1090, 1117). A meta-analytic review by O'Farrell and Fals Stewart (690) found a moderate effect size in 16 controlled trials of behavioral marital therapy. Other marital approaches with significant support were Al-Anon facilitation and disulfiram contracting (168, 248). Similarly, Miller and Wilbourne's box score review (79) found five of eight high-quality studies favored the efficacy of behavioral marital therapy; in contrast, other approaches to marital therapy were found to be effective in only three of eight trials (79). A noteworthy series of trials by O'Farrell and colleagues (225, 236, 238, 690, 961, 1118, 1119) demonstrated not only the efficacy but also the cost-effectiveness of behavioral marital therapy for patients with an alcohol use disorder.

h) Aftercare

Walker et al. (1120) found that involvement in aftercare was a stronger predictor of outcome than length of hospitalization, neuropsychological functioning, or pretreatment drinking and social stability measures. Ouimette et al. (264) found that participation in both aftercare and 12-step groups was associated with better 12-month outcomes in a sample of hospitalized male

veterans. McLatchie and Lomp (1121) randomly assigned patients to mandatory, voluntary, or no aftercare for a 12-week period and found that those who completed aftercare had the lowest relapse rate, with no difference between the mandatory and voluntary groups. Gilbert (1122) randomly assigned patients to one of three aftercare conditions that varied in the degree of the therapist's efforts to maintain the patient in aftercare over 30 appointments. Patients in the maximal effort group were the most likely to complete aftercare, and all who completed aftercare, regardless of their study group, had better outcomes than those who did not. Results from studies that did not include random assignment suggest that greater participation in aftercare is generally associated with fewer drinks on drinking days, but not with diminished frequency of drinking (1655). A controlled study by O'Farrell et al. (225, 1118, 1119) demonstrated that a version of behavioral marital therapy that included relapse prevention techniques (184) and was delivered as an aftercare intervention led to better drinking outcomes. In two separate trials, Kadden and colleagues (223, 1102, 1103) compared inpatient aftercare programs consisting of 1) CBT and coping skills training and 2) insight-oriented interactional group therapy and reported similar outcomes in the two groups. Patterson et al. (1123) found nurse visits delivered over 12 months yielded better abstinence rates than clinical-based review visits. In Project MATCH (43, 265), 12 weeks of individual aftercare treatment using MET, TSF, or CBT showed comparable positive drinking outcomes in a sample of 774 alcohol-dependent patients. Also, 1 of 10 hypothesized matching effects was significant, suggesting that TSF was superior to CBT and MET for patients rated high in the seeking meaning category.

▶ C. MARIJUANA-RELATED DISORDERS

1. Somatic treatments

There have been no successful controlled trials to date of pharmacotherapy for marijuana dependence. Trials with negative results have studied bupropion (1182), divalproex (1183, 1184), naltrexone, and nefazodone (1185). The main active ingredient of cannabis, Δ-9-tetrahydrocannabinol, has been tried in a laboratory study with human research volunteers and found to reverse withdrawal-associated psychomotor performance impairment and weight loss (1184) and warrants further study. No pharmacotherapy trials to prevent marijuana reinstatement after abstinence have been reported.

2. Psychosocial treatments

Given the absence of effective pharmacotherapies for marijuana dependence, the treatment of marijuana-related psychiatric disorders has primarily focused on psychosocial approaches (1178). Controlled trials have used cognitive-behavioral relapse prevention group therapy, social support group treatment, contingency management therapies, motivational individualized assessment and intervention, and MET therapy. However, it is difficult to discuss comparative efficacy across trials because the trials differed methodologically (e.g., in the diagnostic criteria and control groups used, the length of treatment and follow-up, the use of urine toxicology screens to confirm marijuana abstinence, the way in which interventions were delivered). Study samples also differed in their size and ethnic diversity. In general, existing trials consistently support the efficacy of the active treatments being studied.

a) Cognitive-behavioral and relapse prevention therapies

A number of studies in individuals with marijuana-related problems have compared outcomes after motivational or CBT interventions (1178). Stephens et al. (1187) randomized 212 sub-

jects to receive relapse prevention therapy or a social support discussion group intervention. Both treatment conditions were associated with significant reductions in marijuana use relative to baseline, although no significant group differences were found in abstinence rates, marijuana-related problems, or days of marijuana use. Subsequently, 291 subjects were randomized into a delayed-treatment control group, a two-session motivational treatment group, and an intensive (14-session) relapse prevention treatment group (1186). Although no significant differences were observed between the brief and the more intensive treatment, marijuana-related outcomes for the two active treatments were found to be better than those with the delayed-treatment control condition. More recently, a replication and extension of that study involving a multisite trial of 450 marijuana-dependent patients compared three approaches: 1) a delayed-treatment control, 2) a two-session motivational approach, and 3) a nine-session combined motivational and coping skills approach (276). The results suggested that both active treatments were associated with significantly greater reductions in marijuana use than the delayed-treatment control condition at 4- and 15-month follow-up. Moreover, the nine-session intervention was significantly more effective than the two-session intervention, and this effect was sustained to 15-month follow-up.

Copeland et al. (1188) also studied CBT interventions for cannabis dependence, randomly assigning 229 participants to a six-session CBT program, a single-session CBT intervention, or a delayed-treatment control group. Participants in the treatment groups were assisted in acquiring skills to promote cannabis cessation and maintain abstinence. At about 6-month follow-up, both treatment groups reported better outcomes (greater abstinence rates, fewer marijuana use–related problems, less concern about control over marijuana use) than the delayed-treatment control group.

b) Behavioral therapies

Budney et al. (201) applied contingency management to marijuana users. They randomized 60 subjects to receive 4 sessions of MET, 14 sessions of MET in combination with coping skills therapy, or 14 sessions of MET in combination with coping skills therapy and voucher incentives. Although no differences in abstinence rates were noted between individuals receiving 4 sessions of MET or 14 sessions of MET plus coping skills therapy by the end of treatment, greater rates and durations of abstinence were seen in the group receiving MET plus coping skills therapy and voucher incentives. Thus, adding voucher-based incentives to coping skills and MET appears to improve outcomes during treatment for marijuana dependence.

▶ D. COCAINE-RELATED DISORDERS

1. Somatic treatments

a) Medications to treat cocaine dependence

More than 45 different medications have been studied in the search for an effective pharmacological treatment for cocaine dependence (1225). Although a number of studies have shown promising results with a variety of pharmacotherapeutic agents, no medication has been found to have clear-cut efficacy in the treatment of cocaine dependence (1222–1224). Most studies have been hampered by methodological problems, including lack of adequate controls and consistent outcome measures (e.g., urine tests rather than self-reports), failure to standardize the type and "dose" of the accompanying psychosocial interventions, lack of clarity about the importance of craving in the maintenance of cocaine dependence, the role of craving in the natural course of untreated cocaine abstinence syndrome, and lack of agreement as to the exact meaning of the term "craving" (1204, 1209).

(1) Antidepressants

Gawin et al. (1227) found desipramine to be more effective than lithium or placebo in reducing cocaine use by outpatients without a coexisting mood disorder. Other reports (1215, 1230, 1231) failed to confirm these positive findings, possibly because of differences in patient population and route of cocaine administration. A subsequent study of desipramine and placebo with and without psychotherapy showed improvement with desipramine compared with placebo in the short term (6 weeks) but not at 12 weeks or 1 year (503). In buprenorphine-treated patients, desipramine was better than placebo for cocaine use (1228), and in methadone-treated patients, contingency management with desipramine produced more cocaine abstinence than desipramine alone, contingency management alone, or no treatment (1229).

Fluoxetine (1232, 1233) and bupropion (1234) also showed some benefit in small studies but demonstrated no superiority to placebo when evaluated in larger trials (413, 1235–1238).

(2) Dopamine agonists

Dopamine agonists are another class of agents that have been used in the treatment of cocaine dependence. The evidence for amantadine's effectiveness is inconsistent in that efficacy was observed in one controlled trial (1240) but not in two others (1225, 1231). Another controlled trial with amantadine found no overall difference between individuals receiving amantadine and those receiving placebo (1239), although those with more severe withdrawal symptoms appeared to have a better response to amantadine (1226).

The selective MAOI selegiline showed safety and some promise in laboratory studies in humans during cocaine administration, but a recent large multisite study failed to show its superiority to placebo (1241; F. Vocci, personal communication). Evidence for the benefits of L-dopa/carbidopa is limited (1242). Pergolide has been studied in larger trials and shown to have no superiority over placebo (1220, 1243). Laboratory studies in humans have suggested that a dopamine D_1 agonist (ABT-431) might reduce cocaine craving, but no oral formulations are available for outpatient trials (1656, 1657). Finally, replacement therapies using methylphenidate or sustained-release amphetamine have been superior to placebo for patient retention and reduction in cocaine use, but these studies need further replication (1244, 1245, 1247, 1658, 1659).

(3) Opioid-related agents

The mixed opioid agonist-antagonist buprenorphine has shown some promise in open trials in the treatment of patients dependent on both cocaine and opioids (1248, 1249), although three large-scale double-blind, clinical trials comparing patients maintained on buprenorphine with those receiving methadone showed no decrease in cocaine use among the former group (1250–1252). Although work by Schottenfeld et al. (1253) suggests that higher doses of buprenorphine (12–16 mg/day) may be effective, larger-scale clinical trials have found this medication to be effective only in combination with desipramine or, particularly, contingency management (1228, 1229, 1254). Naltrexone has also been tested and shown to be not useful for cocaine dependence (1255).

(4) Other medications

Anticonvulsants and agonists for GABA have been studied with some promise. Initial studies of carbamazepine in the treatment of cocaine dependence yielded some favorable results (1256), but subsequent double-blind, placebo-controlled studies failed to establish the efficacy of this drug in cocaine-dependent patients (1257–1261). A pilot study of the anticonvulsant topiramate showed promise (1262). The GABA$_B$ agonist baclofen has shown some success in treatment (1263), and a recent double-blind clinical trial of tiagabine, a GABA-reuptake blocker, was superior to placebo for reducing cocaine use (1264). Finally, modafinil shows promise for reducing cocaine abuse (1265).

b) Medications to change the subjective effects of cocaine

Attempts to find a medication that blocks or attenuates the subjective (e.g., euphorigenic) effects of cocaine have included trials of neuroleptics (1268, 1269), mazindol (1270), disulfiram, and a cocaine vaccine. At doses that can be tolerated by patients, neuroleptics and mazindol have not been effective (1271–1273). However, recent data with disulfiram have suggested that it may increase the aversive effects of cocaine and reduce its use (1277, 1660). Animal studies have demonstrated that a cocaine vaccine may form sufficient antibodies to reduce cocaine use (1278).

c) Acupuncture

Although it is not a pharmacological treatment, acupuncture is a somatic treatment that has been frequently used in the treatment of patients with a substance use disorder. Two recent randomized, controlled trials, however, one with 412 subjects (1279) and one with 620 subjects (1280), compared auricular acupuncture (which is supposed to be specifically helpful for patients with a substance use disorder) with a needle insertion control condition (sham acupuncture); the latter study also had a relaxation control condition. In both studies, acupuncture was no more effective than the sham acupuncture control or the relaxation condition in reducing cocaine use. The results of these studies, therefore, do not support the use of auricular acupuncture as a sole treatment for cocaine dependence.

d) Pharmacological treatment in individuals with a co-occurring psychiatric disorder

Several focused and reasonably well-controlled studies have examined the use of second-generation antipsychotics as anticraving agents among individuals with schizophrenia who primarily abuse cocaine. A 6-week open-label study showed that compared with patients taking first-generation antipsychotics, those receiving risperidone showed a significant reduction in cue-elicited cocaine craving, relapse to substance use, and symptom severity (401). A double-blind, randomized trial of olanzapine versus haloperidol was conducted with 31 cocaine-dependent patients with schizophrenia (1661). At the study completion, patients treated with olanzapine showed significantly less cue-elicited craving on two of four craving dimensions and fewer relapses compared with those treated with haloperidol.

2. Psychosocial treatments

a) Cognitive-behavioral therapies

A number of randomized clinical trials among several diverse cocaine-dependent populations have demonstrated that 1) compared with other commonly used psychotherapies for cocaine dependence, CBT appears to be particularly more effective with more severe cocaine users or those with co-occurring disorders (229, 452, 503, 1289, 1292, 1293); 2) CBT is significantly more effective than less intensive approaches that have been evaluated as control conditions (267, 1288); and 3) CBT is as effective or more effective than manual-guided disease-model approaches (267, 1289). Moreover, CBT appears to have a particularly durable impact, with patients continuing to reduce their cocaine use even after they leave treatment (1275, 1290, 1291, 1662).

b) Behavioral therapies

(1) Contingency management

Perhaps the most exciting findings pertaining to the effectiveness of behavioral treatments for cocaine dependence have been the reports by Petry et al. (188) and Higgins et al. (191–194) on the use of behavioral incentives for abstinence. The strategy of Higgins's group has four organizing features that are grounded in principles of behavioral pharmacology: 1) drug use and abstinence must be swiftly and accurately detected, 2) abstinence is positively reinforced,

3) drug use results in loss of reinforcement, and 4) emphasis is placed on the development of reinforcers to compete with drug use (1294). In this approach, urine specimens are required three times a week to systematically detect all episodes of drug use. Abstinence, verified through drug-free urine screens, is reinforced through a voucher system in which patients receive points redeemable for items consistent with a drug-free lifestyle (e.g., movie tickets, sporting goods).

In a series of well-controlled clinical trials, Higgins's group has demonstrated high rates of acceptance, retention, and abstinence in patients receiving this approach, as compared with standard counseling oriented toward 12-step programs (191, 192). Rates of abstinence do not decline substantially when less valuable incentives are substituted for the voucher system (192). The value of the voucher system itself, as opposed to other program elements, in producing good outcomes was demonstrated by comparing the behavioral system with and without the vouchers (193). Although the strong effects of this treatment declined somewhat after the contingencies were terminated, the voucher system has been shown to have durable effects (194). Moreover, the efficacy of a variety of contingency management procedures (including vouchers, direct payments, and free housing) has been replicated in other settings and samples, including cocaine-dependent individuals within methadone maintenance (195, 1295), substance-abusing homeless individuals (1297), freebase cocaine users (1298), and pregnant drug users (1299).

These findings are of great importance because contingency management procedures are potentially applicable to a wide range of target behaviors and problems, including treatment retention and adherence with pharmacotherapy (e.g., retroviral therapies for individuals with HIV). For example, Iguchi et al. (202) showed that contingency management can be effective in reinforcing desired treatment goals (e.g., looking for a job) in addition to abstinence.

In a line of research attempting to reduce the costs of contingency management, Petry and colleagues (204, 205) demonstrated that a variable ratio schedule of reinforcement that provides access to large reinforcers but at lower probabilities is effective in retaining subjects in treatment and reducing substance use. Rather than earning vouchers, subjects earn the chance to draw from a bowl and win prizes of varying magnitudes. The prizes range from small $1 prizes (e.g., bus tokens, McDonald's coupons) to large $20 prizes (e.g., portable radios, watches, and phone cards) to jumbo $100 prizes (e.g., small televisions). This system is far less expensive than the standard voucher system because only a proportion of behaviors are reinforced with a prize. In a study of 42 alcohol-dependent veterans who were randomly assigned to standard treatment or standard treatment plus contingency management, 84% of the contingency management subjects were retained in treatment throughout an 8-week period compared with 22% of standard treatment subjects. By the end of the treatment period, 69% of those receiving contingency management had not experienced a relapse to alcohol use, but only 39% of those receiving standard treatment were abstinent (205); there were similar findings among cocaine abusers (204).

(2) Cue exposure treatment
Cue exposure therapy has also been used in the treatment of cocaine use disorders, with equivocal results (189).

c) Psychodynamic and interpersonal therapies
No randomized clinical trials have been conducted for psychodynamically oriented treatments for cocaine abuse or dependence. A case series of patients successfully treated with individual psychodynamically oriented psychotherapy was reported by Schiffer (1300), and there is a preliminary report revealing a high rate of retention with modified psychodynamically oriented group psychotherapy (1301). Spitz (1302) has also described the use of group therapy for this population.

d) Self-help groups and 12-step-oriented treatments

Several trials have evaluated manual-guided professionally delivered treatments, including TSF (268) and individual drug counseling (269), that enhance a patient's motivation to participate in 12-step programs. As part of these professional treatments, patients are actively encouraged (but not required) to attend Narcotics Anonymous or Cocaine Anonymous meetings, become involved in traditional fellowship activities, and maintain journals of their self-help group attendance and participation.

In a comparison of TSF, CBT, and clinical management (a supportive approach in which patients received comparable empathy, support, and other "common elements" of psychotherapy but none of the unique "active ingredients" of TSF or CBT) for alcoholic cocaine-dependent individuals, TSF was found to be significantly more effective than clinical management and was comparable with CBT in reducing cocaine use (267). In addition, results at 1-year follow-up suggested that gains from treatment were maintained for subjects who received TSF or CBT; these subjects reported continuing to reduce their cocaine use throughout the follow-up period compared with subjects who received clinical management. Moreover, there was a strong association between the attainment of significant periods of abstinence during treatment and abstinence during follow-up, which emphasizes that the inception of abstinence, even for comparatively brief periods, is an important goal of treatment (194, 1275).

The results of the NIDA Collaborative Cocaine Treatment Study, a multisite randomized trial of psychotherapeutic treatments for cocaine dependence (219, 1305), suggest the effectiveness of a similar approach: 12-step-oriented individual drug counseling (269). In that study, 487 cocaine-dependent participants in four sites were randomly assigned to one of four conditions: 1) cognitive therapy (1306) plus group drug counseling; 2) supportive-expressive therapy, a psychodynamically oriented approach (217) plus group drug counseling; 3) 12-step-based individual drug counseling plus group drug counseling; or 4) group drug counseling alone. The treatments offered were intensive (36 individual and 24 group sessions over 24 weeks, for a total of 60 sessions) (219). On the whole, outcomes were good, with all groups significantly reducing their cocaine use from baseline; however, the best outcomes were seen for subjects who received individual drug counseling.

McKay et al. (229) compared 12-step-oriented standard group counseling to relapse prevention aftercare in 98 cocaine-dependent patients. Rates of complete abstinence in the 6-month study period were higher in the standard group counseling group than in the relapse prevention group, whereas relapse prevention was more effective in limiting the extent of cocaine use in those who currently used cocaine. Overall effectiveness was judged to be equivalent for the two treatments.

The studies above evaluated professional treatments based on 12-step concepts and not participation in self-help groups, per se. The literature on participation in Cocaine Anonymous or other 12-step self-help groups is more limited than that for patients with an alcohol use disorder participating in AA. In one study of day hospital rehabilitation for patients with a cocaine use disorder (1304), greater participation in self-help programs 3 months after treatment predicted less cocaine use 6 months after treatment, even after pretreatment patient characteristics and degree of success in the day hospital program were controlled for in the study.

Self-help groups have not been shown to be a sufficient alternative to professional treatment. For example, a large randomized trial that directly compared referral to self-help with professional treatments found poorer outcomes, with high rates of treatment utilization for the patients referred to self-help compared with inpatient treatment (1303).

E. OPIOID-RELATED DISORDERS

1. Somatic treatments

a) Opioid agonist therapies

(1) Methadone

Methadone is the most thoroughly studied and widely used pharmacological treatment for opioid dependence. Studies of its efficacy and safety have focused on its use as a maintenance medication and a medication for the treatment of opioid withdrawal. This section will review studies of methadone's efficacy and safety for these two purposes.

a. Use of methadone as a maintenance agent

Studies of methadone's efficacy and safety fall into two general categories: controlled clinical trials and naturalistic/survey studies. When designed and conducted properly under controlled conditions that are related to but distinct from routine clinical practice, clinical trials provide evidence of methadone's efficacy. The scientific value inherent in the methods of such studies (e.g., double-blind dosing) is offset by the somewhat unusual experimental conditions of a clinical trial (e.g., intensive monitoring of participants). Naturalistic survey studies of methadone provide complementary evidence to clinical trials and typically report results for larger populations that have been treated in routine settings. There is little control for factors such as expectancy, but these studies do provide data that are more closely tied to real-world clinical settings.

1) Naturalistic/survey studies of methadone treatment

Examples of naturalistic/survey studies of methadone efficacy include the Drug Abuse Reporting Program (61), the Treatment Outcome Prospective Study (1399), the Drug Abuse Treatment Outcome Study (45, 73, 1663), and the Effectiveness of Methadone Maintenance Treatment Study (169). The first three of these survey studies assessed methadone treatment as one of several substance abuse treatment modalities. Participants in these projects were not randomized to a treatment modality, and services were given in routine clinic settings and were not delivered in a blinded fashion. Results from such studies generally showed that methadone is effective when post- and pretreatment functioning are compared and that better outcomes are associated with longer periods of treatment. However, the relative efficacy of different doses of methadone has generally not been addressed in such survey studies.

The Effectiveness of Methadone Maintenance Treatment Study (169) was somewhat different from these national survey studies, as it assessed methadone treatment in a relatively restricted geographic region—six clinics located on the East Coast (two each in New York, Philadelphia, and Baltimore). However, the study did provide intensive evaluation of a large number of patients treated specifically with methadone (versus a more heterogeneous population of patients in the other surveys). A total of 617 patients were initially assessed; of these, 126 were new methadone admissions, 346 were in treatment for <4.5 years, and 145 were in treatment for ≥4.5 years.

At the 1-year follow-up, the methadone dose was inversely related to self-reported heroin use in the 30 days prior to the interview. The study found that longer time in treatment was associated with decreased rates of intravenous drug use. For patients in treatment for 4 years, self-reported use declined from 81% at the time of admission to 29% after 4 years. Among patients who had been in treatment for ≥4.5 years, 92% reported no heroin use and 83% reported no cocaine use in the 30 days before the study assessment. Other factors besides methadone dose were also found to be related to treatment and outcome in this study, such as the level of involvement of the clinic director.

Other naturalistic studies of methadone treatment provide further evidence of methadone's efficacy, especially with regard to methadone dose. For example, one study of 652 methadone maintenance patients found that heroin use was greatest among those with daily methadone maintenance doses <70 mg/day and that, independent of dose, time in treatment was associated with less heroin use (1664). Similarly, a review of methadone dosing for 62 patients treated in an Australian clinic found that higher doses were associated with less heroin use (1665). This study also concluded that the relative odds of heroin use were reduced by 2% for every 1 mg increase in maintenance dose.

It is important to note that an inherent weakness to survey studies is that patients are not randomly assigned to the conditions being compared. There may be other patient or program characteristics besides methadone dose or time in treatment that may account for the differences seen in such studies. In addition, these studies often rely on patient self-reports of substance use, including retrospective assessments of past use that are then used to calculate changes over time. Expectancy effects may also play an important role in outcomes seen. Thus, although survey studies can be helpful and informative, these and other liabilities compromise the degree of certainty that can be assigned to their conclusions.

2) Clinical trials of methadone dose and treatment

Numerous clinical trials have tested methadone for the treatment of opioid dependence. In general, these studies have found that methadone medication is a safe and effective pharmacotherapy for the treatment of opioid dependence and that methadone combined with other services such as counseling, behavioral interventions, and urine monitoring can broaden the efficacy of this intervention to include a greater range of treatment outcomes such as increased prosocial behavior and decreased nonopioid substance use.

There have been two double-blind, placebo-controlled studies of methadone for the treatment of opioid dependence. The first was conducted in Hong Kong in the early 1970s and enrolled 100 male opioid-dependent patients who were initially hospitalized for 2 weeks and treated with 60 mg/day of methadone (1666). Participants were then randomly assigned to 1) the placebo condition, in which they underwent 1-mg dose reductions of methadone each day on an outpatient basis and then were maintained on placebo after 60 days, or 2) the maintenance condition, in which they could have outpatient dose adjustments with a maximum possible dose of 130 mg/day. For this latter group, the average dose was 97 mg/day (range 30–130 mg) after 1 year. Subjects were withdrawn from the study if they missed 6 consecutive weeks of treatment or had six consecutive opioid-positive urine samples. At the 32-week evaluation point, 10% of placebo-treated patients remained in treatment (most of the rest having been withdrawn because of urine evidence of persisting illicit opioid use) compared with 76% of maintenance patients.

The second placebo-controlled study of methadone treatment was conducted in the late 1980s in Baltimore, Maryland, and enrolled 247 opioid-dependent outpatient participants (1350, 1351). The study began by randomly assigning subjects to one of three fixed doses of oral methadone (0, 20, or 50 mg/day). Participants were required to attend the clinic daily for supervised dose ingestion and were discharged for missing 3 consecutive days of treatment. Primary outcomes were treatment retention and urine test results. At the end of the 20-week study, significant differences were found among the three groups for treatment retention (primarily between the 50- and 0-mg groups), with the 20-mg group generally doing better than the 0-mg group. In addition, there were significantly lower rates of opioid-positive urine test results for the 50-mg group compared with the other two groups. A variety of secondary outcome measures, such as self-reported illicit opioid use, also showed dose-related effects. In addition to the demonstrated dose-related efficacy of methadone, these study results also indicated that the 20-mg dose of methadone might keep some patients in treatment but was not

as effective in decreasing illicit opioid use as the 50-mg dose. Study limitations included the use of fixed doses of methadone and the absence of a dose condition ≥50 mg/day.

Further controlled clinical trials of methadone have tested higher versus lower doses of methadone. For example, a 40-week multicenter VA outpatient study of LAAM for the treatment of 430 opioid-dependent males included two fixed methadone dose control conditions of 50 and 100 mg/day (1349). The induction procedure for the 288 methadone-treated subjects was relatively slow; subjects were started on 30 mg of methadone per day and received 10-mg dose increases once per week until the target dose was achieved. Induction, therefore, lasted 5 weeks longer for patients in the 100-mg versus the 50-mg methadone group. Urine samples were collected and tested once per week, and the results were summarized using a set of rules that weighted results based on when the sample was collected and how missing values were handled. Outcomes for the methadone-treated subjects showed higher opioid urine scores (poorer outcomes) for the 50-mg versus the 100-mg group. Although this study provided evidence of methadone's dose-related efficacy on illicit opioid use, its results are limited by its use of an all male population, a slow induction procedure, fixed doses, and a somewhat unusual method for summarizing urine test results.

Another outpatient study compared a moderate dose (40–50 mg/day; N=97) with a higher dose (80–100 mg/day; N=95) of methadone for the treatment of opioid dependence (1352). This 40-week double-blind, randomized trial used a flexible dosing procedure in which participants could receive dose increases based on evidence of continued illicit opioid use. Primary outcome measures were treatment retention, the results of twice-weekly urinalyses, and self-reported illicit opioid use. The results showed no significant difference in treatment retention for the two groups but found a significantly lower rate of opioid-positive urine samples for the higher-dose condition. Both groups had marked declines in self-reported illicit opioid use, with significantly less use by the high-dose versus the moderate-dose group. Although significant effects were found on some outcomes in this study, both doses produced clinically meaningful decreases in illicit opioid use. The lack of difference between the study groups for treatment retention suggests that there may be a plateau in the dose-related efficacy of methadone in maintaining patients in treatment but not in decreasing illicit opioid use for the doses tested. However, the schedule of twice-weekly urinalyses used in this study may have failed to capture all illicit opioid use occurring in the study population.

Other controlled trials of methadone treatment and methadone dosing have also been conducted (1250, 1251, 1667–1670). In general, these studies have shown that methadone has dose-related efficacy, although it is important to note that not all randomized double-blind methadone studies have shown such an effect. However, it is also important to note that no double-blind, randomized, controlled clinical trials have tested daily doses of methadone ≥100 mg/day. There have been single-blind and open studies of higher doses of methadone that were conducted primarily in the early years of methadone treatment (1671–1673), and reports from clinical practice in both the United States and other countries indicate higher doses of methadone are used by some clinicians (1342–1346). Currently, there is no research database that provides information about the relative efficacy and safety of higher doses (i.e., ≥100 mg/day) of methadone.

b. Use of methadone as a withdrawal (detoxification) agent
The number of studies examining methadone for treating opioid withdrawal is more limited than the number examining methadone in maintenance treatment of opioid dependence. Outcomes from methadone withdrawal are generally poor (1674–1676), especially when compared with the success associated with methadone maintenance treatment. These studies have examined the various parameters under which methadone tapering can occur in an effort to determine optimal withdrawal schedules.

An early double-blind, randomized, outpatient study of methadone withdrawal by Senay et al. (1677) used a four-group design: dose reductions of 10% per week for 10 weeks, reductions of 3% per week for 30 weeks, stable dosing with patients knowing their dose would not change, and double-blind stable dosing. The 127 study participants were in methadone maintenance treatment, with an average dose of 31 mg/day. They could request a 1-week dose halt or increase during their withdrawal. Results from the study showed the poorest outcomes occurred for patients in the rapid dose-reduction (10% per week) group as measured by taper interruptions, positive urine sample rates, and withdrawal symptom complaints. As a group, patients undergoing the rapid withdrawal essentially stabilized around an average of 10 mg/day of methadone due to their requests for dose halts and temporary dose increases. These results suggested that a more gradual methadone taper (3% per week) leads to better outcomes than a more rapid taper (10% per week), although methadone maintenance treatment is even more effective.

Another randomized clinical trial compared methadone withdrawal—120 days of methadone induction/stabilization followed by a 60-day withdrawal and then 8 months of nonmethadone treatment—to 14 months of maintenance treatment in 179 opioid-dependent patients (1678). The study was not conducted in a blinded fashion, and the withdrawal group had more nonpharmacological services available to them. Results from the study showed significantly better treatment retention for the maintenance group but similar rates of illicit opioid use for the two groups until month 5, when patients withdrawn from methadone began to have higher rates of illicit opioid use. These study results support the value of methadone for maintenance treatment compared with withdrawal from methadone, although certain qualifiers to the study should be noted: expectancy effects could contribute to the outcomes shown, the requirement that withdrawn patients attend more groups and counseling may have contributed to the high dropout rate, and the length of the withdrawal (60 days) may have been too quick, as suggested by the results from the Senay et al. study (1677) reviewed above.

Other studies of methadone withdrawal have been conducted but generally with smaller sample sizes or in atypical treatment settings (e.g., inpatient units) that make their results limited in their applicability to current treatment circumstances. For example, an inpatient study of a 10-day methadone withdrawal comparing a linear schedule of daily dose reductions (based on a fixed percentage of the starting dose) to an exponential schedule of daily dose reductions (based on a percentage of the previous day's dose) found no differences in the time course of withdrawal symptoms, peak symptom severity, and patient adherence (1679). Other studies (1675, 1677, 1680) examining whether or not informing patients about their methadone dose-reduction schedule influences treatment outcome have concluded that informed patients have better outcomes. There is some evidence that patients do not have better outcomes, however, if they, rather than clinicians, are allowed to control their methadone withdrawal schedule (1675, 1681). Finally, one study found that lower rates of illicit opioid use occurred when patients received voucher incentives for opioid-negative urine samples during methadone withdrawal, although it appears this intervention primarily delayed relapse to illicit opioid use (1682).

c. Safety and side effects of methadone

Like all mu agonist opioids, overdose with methadone can produce respiratory depression and death. When used under physician supervision, methadone is a safe medication with limited side effects. Constipation, sweating, sexual dysfunction, and sedation are the most commonly reported side effects. When patients first start on methadone, they may experience some side effects (e.g., sedation) to which they will develop a tolerance. The two most common side effects reported by patients, constipation and sweating, may persist despite chronic treatment on a stable dose. Small effects that are not clinically significant have been noted on some physiological measures assessed during chronic methadone dosing (e.g., heart rate, pupil diameter) (1359, 1683). Studies of chronic dosing with methadone have shown no evidence of organ damage, such as hepatotoxic effects (1684–1686). There have been case reports of high-dose

methadone treatment associated with torsade de pointes and a prolonged corrected QT interval (1687–1689). Methadone-related increases in the corrected QT interval appear to be related to dose (1690–1692), and patients experiencing this problem often have had other risk factors for torsade de pointes.

Early studies of psychomotor and cognitive performance tasks in methadone-maintained patients showed no significant impairments (1356–1358), but more recent studies have shown significantly poorer performance on these tasks in methadone-maintained patients versus matched control subjects (1359, 1360). Whether such effects are due to the acute or chronic effects of methadone or to other factors associated with a long history of substance use is not entirely clear despite efforts in these more recent studies to carefully match patients.

(2) LAAM

LAAM is an opioid agonist medication that has effects similar to those of methadone but a longer duration of action. LAAM has demonstrated efficacy as a maintenance agent in large multisite, randomized, double-blind studies (1349, 1693); smaller randomized, double-blind studies (1667, 1694–1696); and nonblind clinical trials (1697–1705). It also appears to be effective as a withdrawal (detoxification) agent (1674, 1706). Clinical trials with LAAM reported typical opioid agonist side effects (1349, 1707) but no cases of deaths or other significant adverse events that seemed linked to LAAM use. However, later case reports of corrected QT interval (QTc) prolongation and torsade de pointes (1337) led to LAAM's withdrawal from the U.S. and European markets.

(3) Buprenorphine

Clinical studies of buprenorphine have used two different formulations: solution and tablets. Because of its poor oral bioavailability, most clinical trials of buprenorphine for the treatment of opioid dependence have used a sublingual, often alcohol-based, solution. A liquid sublingual form of buprenorphine, however, was felt to be an impractical long-term treatment option, and as the evidence for its efficacy and safety in the treatment of opioid dependence grew, a water-soluble sublingual tablet form of buprenorphine was developed. However, the tablet form of buprenorphine appears to have lower bioavailability compared with the alcohol-based solution form (1708–1710), suggesting dosing parameters from clinical trials should be interpreted with caution if the solution form of buprenorphine is used.

Because buprenorphine can be abused (1711–1716), it is possible for the sublingual tablet to be dissolved and used parenterally. In France, where buprenorphine is the primary medication used for the treatment of opioid dependence, there have been reports of abuse of buprenorphine tablets (1713, 1717–1719). For this reason, a formulation that combines buprenorphine with naloxone was developed for the U.S. market. Naloxone has poor sublingual bioavailability (1361), so use of this combination tablet sublingually would produce a predominant buprenorphine effect. However, if an opioid-dependent individual dissolved and injected the combination tablet, he or she would risk precipitating a withdrawal syndrome due to naloxone's good parenteral bioavailability. Studies of the combination buprenorphine-naloxone tablet have confirmed such differential effects to be a function of the route of administration (1720–1724). Although the combination tablet is the more commonly used form of this medication, many clinical trials have used a monotherapy tablet, and the monotherapy tablet is the primary form of sublingual buprenorphine used outside the United States. Under chronic dosing conditions, there may be slightly better bioavailability for the combination versus the monotherapy tablets (1710). However, for a given dose of buprenorphine, there is considerable between-subject variability in buprenorphine blood levels.

a. Use of buprenorphine on a daily basis as a maintenance agent

Numerous randomized, double-blind clinical trials have studied the efficacy and safety of sublingual buprenorphine for the outpatient treatment of opioid dependence. This section reviews the three representative studies that compared buprenorphine with placebo and then provides a more limited review of the many studies that compared buprenorphine with methadone.

The first study was a 16-week multisite double-blind, randomized outpatient clinical trial using four different doses of sublingual buprenorphine solution: 1, 4, 8, and 16 mg/day (1725). The primary goal was to compare the 8- and 1-mg doses, with the 1-mg dose serving as the placebo condition. The study enrolled 736 opioid-dependent patients (about 33% female); primary outcome measures were treatment retention, opioid urinalysis results, craving, and global ratings by staff and patients. Results from the study showed significantly better outcomes for the 8- versus the 1-mg groups on all the primary outcome measures. In general, there was no clear pattern of increased side effects or adverse events for the 8-mg group, with the exception of ratings of constipation (but multiple comparisons were made). Although not the primary purpose of the study, the outcomes also showed dose-related effects for buprenorphine, where 4 mg of buprenorphine was better than 1 mg, 8 mg was better than 4 mg, and 16 mg was better than 8 mg, although these differences were not always robust in their magnitude.

The second study was a double-blind, placebo-controlled study that used a somewhat novel clinical trial design that lasted only 2 weeks (1726). In this study, the 150 male and female participants were fast-tracked into treatment and randomly assigned to 0 (N=60), 2 (N=60), or 8 (N=30) mg/day of sublingual buprenorphine solution. Subjects were informed that they could receive placebo or one of two buprenorphine doses and that after 6 days, they could request to have a blind change to one of the other two conditions. Primary outcomes were the percentage of patients in each condition who remained on their original dose and the percentage of patients in each condition who requested a dose change. Other study outcomes such as opioid urine test results and self-reports of drug use were also provided. This study found that, regardless of dose, a significantly higher percentage of patients in the two active conditions remained on their doses compared with the placebo group. Similarly, a significantly higher percentage of patients in the placebo condition requested a dose change compared with the other two groups, but, once again, there was no significant difference between the two active buprenorphine groups. In an interesting finding, male subjects in the two active buprenorphine groups had a significantly lower rate of opioid-positive urine samples, but there was no difference across the three conditions for female subjects. This study provides an alternative demonstration of the efficacy of buprenorphine compared with placebo.

The third study was an office-based protocol that compared sublingual placebo tablets to active buprenorphine/naloxone (16 mg/4 mg) and buprenorphine alone (16 mg) tablets (1727). This multicenter study enrolled 326 opioid-dependent individuals, and study participation lasted 4 weeks for each volunteer. Subjects received supervised dose administration on weekdays and take-home doses of tablets on weekends. Urine samples were collected thrice weekly. Study enrollment was discontinued early because significant differences between the two active conditions and placebo were found on an interim analysis. For example, rates of opioid-negative urine samples were significantly higher for both active treatment groups compared with the placebo group. After the 4-week period, there was a further period of open-label treatment for purposes of safety assessment; the results from this phase showed that buprenorphine was safe and well tolerated. The results from this study provide further evidence of buprenorphine's efficacy compared with placebo, especially when the tablet form is studied (rather than the solution form used in the previous two studies described).

In addition to these three studies, two others have compared buprenorphine with placebo (1394, 1728). Like the studies previously described, these reports also showed that buprenorphine maintenance is superior to placebo treatment as measured by treatment retention, opioid urine test results, and mortality.

Numerous studies have compared buprenorphine's efficacy and, to a more limited extent, its safety to methadone. These studies have generally been randomized, double-blind, clinical trials conducted at a single site with fixed doses of sublingual buprenorphine solution and oral methadone (137, 1251, 1362, 1668, 1729). Variations on this basic methodological approach include studies that have compared methadone with buprenorphine tablets rather than solution (1730–1732), have used double-blind, flexible-dosing schedules rather than fixed doses of methadone and buprenorphine (74, 1363, 1364), or have compared thrice-weekly buprenorphine to daily methadone (74). Some of these studies had relatively small groups of subjects (1364, 1730), although other features of these studies may represent important methodological advances in this line of research.

In general, these studies comparing buprenorphine with methadone demonstrated that outcomes for the two medications can be very similar. An important qualification to this conclusion is that it is not always clear that the studies used comparable doses of the two medications. For example, a study comparing a very low fixed methadone dose with an average fixed buprenorphine dose could lead to the conclusion that buprenorphine is more effective than methadone, but such a study would be a comparison of dose efficacy rather than medication efficacy. When studies have used flexible doses, compared doses of methadone and buprenorphine that are thought to be approximately equivalent, or used more than one fixed dose of each medication for comparison, they have generally found similar outcomes on measures of treatment retention and rates of opioid-positive urine samples for buprenorphine and methadone. However, it appears that based on these studies, buprenorphine's maximal therapeutic effect occurs in the range of 8–16 mg/day of sublingual tablets, which is equivalent to outcomes seen with daily doses of about 50–60 mg of methadone.

b.   Use of buprenorphine on a less than daily basis as a maintenance agent

Buprenorphine's long duration of action suggests that it may be effective on a less than daily basis. Clinical trials of intermittent buprenorphine dosing have typically stabilized patients on a daily dose and then switched them to a less than daily schedule where buprenorphine was administered on active dosing days and placebo was given on the other days. In some studies, buprenorphine doses were not increased (1733, 1734), whereas in other studies the dose was doubled (1367, 1735) on active dosing days. Although there is some evidence that significant withdrawal can occur if the daily dose is not increased when switching to intermittent dosing (1733), increasing the dose to compensate for the 48-hour interdose period generally provides adequate effects for patients and is preferred to daily dosing (1367).

There are several studies of intervals between active doses that are ≥48 hours. For example, a study where triple the daily buprenorphine maintenance dose was administered to patients every 72 hours found some mild increase in opioid agonist effects in the first 24 hours and some mild withdrawal at 72 hours, but neither effect was robust or clinically significant (1368). Similar results were reported in another study testing buprenorphine's effects over a 72-hour time interval (1366). A double-blind study examining a quadruple daily maintenance dose of buprenorphine given at up to 96-hour intervals (1369) did not find excessive opioid agonist effects 24 hours after the quadrupled dose and only mild withdrawal effects at 96 hours. A follow-up open report on double, triple, and quadruple buprenorphine doses for 48-, 72-, and 96-hour intervals, respectively, found similar tolerability of the 96-hour interval as well as a preference by patients for all intermittent, rather than daily, dosing schedules of buprenorphine (1368). These results suggest dosing with buprenorphine on every fourth day is clinically possible, with no significant adverse effects from the higher doses of buprenorphine and comparable efficacy with daily dosing. However, findings from studies that have tested even longer intervals between active buprenorphine doses suggest that 96 hours may be the upper limit of the interdose interval (1736, 1737). In these studies, significant but clinically mild opioid agonist effects were noted 24 hours after the quintuple or sextuple dose, with clinically mild withdrawal effects appearing after 96

hours. Studies have not tested if higher doses of buprenorphine, such as seven times a daily dose, might be effective and safe for shorter periods such as 5 days.

One of the largest controlled clinical trials of intermittent buprenorphine dosing was a double-blind, randomized study comparing thrice-weekly to daily buprenorphine dosing (1738). This study assigned 92 opioid-dependent outpatients to receive sublingual buprenorphine solution daily or sublingual buprenorphine solution on Tuesdays, Fridays, and Sundays and placebo on the other four days. The daily buprenorphine dose was 16 mg/70 kg, whereas buprenorphine dosing in the intermittent condition was 34 mg/70 kg on Friday and Sunday and 44 mg/70 kg on Tuesday. The 72-hour dosing interval was from Tuesday to Friday to avoid potential study confounders associated with the weekend. There were no differences in rates of opioid-positive urine tests, self-reports of illicit opioid use, treatment retention, and medication adherence between the two groups and no significant adverse events noted for either group. The results from this large controlled study suggest that intermittent buprenorphine can be as equally effective as daily buprenorphine.

Although the studies reviewed here have all used the solution form of buprenorphine, there have also been studies of intermittent dosing with buprenorphine tablets. One double-blind outpatient clinical trial compared daily dosing of 8-mg buprenorphine tablets to thrice-weekly dosing with 16-mg tablets on Mondays and Wednesdays, 24-mg tablets on Fridays, and placebo tablets on the four nonactive dosing days. The study found equivalent retention for the two groups but a higher rate of opioid-positive urine samples in the intermittent dosing group (1739). Using the buprenorphine/naloxone combination tablets, Another study showed that patients prefer thrice-weekly take-home doses of the medication to both daily and thrice-weekly medication visits at a clinic (1740). These two studies provide evidence of the practicality of using buprenorphine tablets on an intermittent basis.

c.   *Use of buprenorphine as a withdrawal (detoxification) agent*
Controlled clinical trials and reports of buprenorphine for the treatment of opioid withdrawal have varied in several ways. Some withdrawal studies have compared buprenorphine with methadone (1741), whereas others have compared it with clonidine (1393, 1742, 1743). Different formulations of buprenorphine (1384, 1744) and rapid or prolonged withdrawals (1392, 1745, 1746) have also been used in these studies. There has been some interest in and research on using buprenorphine as a bridging agent to treatment with naltrexone (1745, 1747). Several reports of buprenorphine's use in opioid withdrawal are open studies describing clinicians' experience with buprenorphine (1384, 1748–1752). Although the outcomes noted in these reports are confounded by the lack of important features found in appropriately conducted clinical trials, they do provide important clinical evidence of buprenorphine's acceptability as a withdrawal medication.

An early double-blind, double-dummy, random-assignment, outpatient clinical trial compared fixed doses of sublingual buprenorphine solution with oral methadone in the treatment of opioid withdrawal (1741). A total of 45 heroin-dependent male subjects were stabilized on 30 mg of methadone or 2 mg of buprenorphine for 3 weeks, underwent a dose taper for 4 weeks and then received placebo for 6 weeks. A novel feature to this study's design was that subjects underwent a 6-mg hydromorphone challenge session during the second week of stabilization (to test the relative blockade efficacy of the two treatment medications). Results from the withdrawal assessments showed the two medications were quite similar on measures of treatment retention, drug use, and rating of withdrawal. However, results from the hydromorphone challenge sessions showed that methadone produced significantly greater blockade than buprenorphine. The results from this early buprenorphine withdrawal study demonstrate that similar outcomes can be achieved with these two medications, although the study used relatively low doses of both medications and the overall results showed poor outcomes for both groups.

An inpatient, randomized, double-blind clinical trial compared sublingual buprenorphine solution to oral clonidine in a relatively short opioid withdrawal procedure (1742). In this study of 25 opioid-dependent male and female patients, participants received 3 days of a fixed-dose schedule of buprenorphine or a 5-day fixed-dose schedule of clonidine. Because this was an inpatient study, reports of withdrawal symptoms were not confounded by illicit substance use. Overall, patients treated with buprenorphine were found to have less opioid withdrawal than those treated with clonidine, whereas there was more hypotension in patients treated with clonidine. This study demonstrated that sublingual buprenorphine was more effective than clonidine in the inpatient treatment of opioid withdrawal; other studies and reports comparing buprenorphine with clonidine have shown similar results (1384, 1391–1393).

A large double-blind, randomized, outpatient clinical trial compared withdrawal using buprenorphine with clonidine and clonidine plus naltrexone in an outpatient primary care clinic setting (1747). This study randomly assigned 162 opioid-dependent male and female patients to one of three conditions: sublingual buprenorphine for 3 days, followed by clonidine and naltrexone; 7 days of clonidine; or 7 days of clonidine plus naltrexone. Results from the study showed that treatment retention was not significantly different for the three groups. However, there were significantly less opioid withdrawal symptoms (both overall withdrawal and peak effects) for buprenorphine-treated patients compared with the other two groups. These study results give further evidence of the clinical value of buprenorphine compared with clonidine provided on an outpatient basis.

d. Safety and side effects of buprenorphine

Buprenorphine has been extensively tested in a variety of outpatient clinical trials, with no reports of significant adverse events from these studies. In addition, it has been used extensively in other countries, especially France, where it is estimated that there are over 70,000 buprenorphine-treated patients.

There is some evidence that buprenorphine may have effects on hepatic function. One report, based on a retrospective review of 120 patients treated with sublingual buprenorphine, suggested that buprenorphine is associated with elevated results on liver function tests for some patients with a history of hepatitis (1753). Although these elevations were relatively mild, there is also evidence that intravenous use of buprenorphine can produce marked increases in liver function test values (1754, 1755). One inpatient study of buprenorphine also found mild increases in liver transaminases over time, although the lack of a control group, the nonspecificity of these laboratory results, and the relatively mild effects seen make interpretation of such findings difficult (1756).

Systematic evaluations of buprenorphine's other side effects have been relatively scarce. One report by Lange et al. (1756) on safety and side effect measures collected during a 12-week inpatient study of buprenorphine induction as well as a study on daily versus alternate-day dosing (1733, 1757) found that no symptoms were rated as definitely related to buprenorphine; the only two symptoms rated as probably related to buprenorphine were drowsiness/sedation and, most frequently, constipation. Nausea/vomiting and headache, which occurred in the first 1–2 weeks of treatment, were rated as possibly related to buprenorphine. A second report that compared safety and side effect measures from a clinical trial comparing daily buprenorphine solution to daily oral methadone found that there were few significant differences in side effect reports from the two medications (1758). However, as was found in the Lange et al. (1756) study, ratings of constipation were higher for the buprenorphine versus the methadone group, although they were relatively low for both groups.

Available evidence varies with respect to mortality and serious adverse events such as respiratory depression associated with buprenorphine. Because of buprenorphine's unusual pharmacological profile, which includes a bell-shaped dose-response curve observed in preclinical studies (1759–1761), it has been thought that overdose with buprenorphine would have a low

likelihood of producing significant respiratory depression. Indeed, there have been at least two case reports of buprenorphine overdose in which patients did not experience respiratory depression (1762, 1763). However, there have also been case reports from France of deaths associated with buprenorphine use, typically when buprenorphine was injected in combination with a benzodiazepine, most typically flunitrazepam, which is not available by prescription in the United States (1764, 1765). There is also preclinical evidence that the combination of buprenorphine and a benzodiazepine can cause respiratory depression (1766) and evidence that suggests the interaction of buprenorphine with flunitrazepam is due to pharmacodynamic rather than pharmacokinetic effects (1767). Finally, benzodiazepine abuse is not uncommon in opioid-dependent patients in the United States; in one outpatient clinical trial of buprenorphine-treated patients, 6.2% of the patients' urine samples were positive for benzodiazepines (1363). However, buprenorphine-related deaths in U.S. clinical trials were not found, suggesting that use of buprenorphine as prescribed, even when combined with illicit benzodiazepine use, is typically not associated with fatalities. However, more liberal availability of buprenorphine in the United States could lead to deaths as has been seen in France.

b) Opioid antagonist therapy: naltrexone

Naltrexone is the only opioid antagonist medication currently approved in the United States for the maintenance treatment of opioid dependence.

(1) Efficacy of naltrexone as a maintenance agent

Naltrexone's efficacy in the treatment of opioid dependence has been studied under two general experimental designs: the inpatient human laboratory and outpatient clinical trials.

a. Naltrexone's efficacy as demonstrated in human laboratory studies

Studies of naltrexone in the human laboratory setting have typically withdrawn opioid-dependent volunteers from opioids and then tested the acute effects of opioids while maintaining the subjects on naltrexone. Under such conditions, naltrexone has been shown to be effective in blocking the effects of acute opioid use (145, 1768–1772).

In one study, for example, 12 heroin-dependent inpatients were withdrawn from opiates and then maintained on 50 mg/day of naltrexone (N=3) or daily placebo (N=9) (1372). The subjects were then allowed to self-administer four doses of heroin each day over the next 10 days. At the end of the study, the placebo group self-administered significantly more doses of heroin than did the naltrexone group. The naltrexone group self-administered heroin six times over the 10 days, whereas every placebo-maintained subject took heroin at least twice per day and three of the nine took all available heroin over the 10-day period. Results such as these demonstrate that naltrexone can be highly effective in blocking the effects of short-acting opioids such as heroin.

b. Naltrexone's efficacy as demonstrated in clinical trials

There have been numerous reports on clinician experience with the use of naltrexone in the outpatient treatment of opioid dependence (1773–1779). Large, double-blind, placebo-controlled studies of naltrexone are more uncommon, partly because maintaining the blind in an outpatient study of naltrexone is virtually impossible. Participants can easily guess their condition assignment if they use opiates and feel or do not feel an effect.

One of the earliest and still one of the largest double-blind studies comparing naltrexone with placebo for the treatment of opioid dependence illustrates the difficulties in such clinical trials (1375). This multisite study enrolled 735 patients who were recently withdrawn from illicit opioids, maintained on but withdrawn from methadone prior to receiving the study medication, or withdrawn from opioids and participating in drug-free treatment. The attrition rate for this study was high, with 543 (74%) participants dropping out before receiving any study medication. Of the 192 who received medication, 170 (89%) dropped out before com-

pleting the 9-month study, with >50% dropping out in the first 2 months of the study. For participants who submitted at least five urine samples, there was no significant difference in rates of opioid-positive urine samples. However, an analysis of a subgroup of patients who had at least one opioid-positive urine sample, implying they would have experienced naltrexone's beneficial effect or placebo's lack of effect, found a significantly lower rate of opioid-positive urine samples in the naltrexone-treated (N=17) versus the placebo-treated (N=18) group. This study, which sought to test the overall acceptability and efficacy of naltrexone treatment, showed there could be some possible efficacy in a small group of patients and concluded that this group is most likely to be those who are already in drug-free counseling and who have a high level of motivation.

Voucher incentives have been shown to improve patient adherence with naltrexone treatment (1406, 1407), and improved adherence implies that there should be less illicit opioid use. In the study by Preston et al. (1406), for example, 58 naltrexone-treated patients were randomly assigned to a contingent group where voucher incentives were given for each naltrexone dose taken (N=19), a noncontingent group where voucher incentives were given unsystematically and independent of medication adherence (N=19), or a no-voucher group (N=20). Comparing illicit opioid use among the three groups was extremely difficult because the group receiving vouchers contingent on adherence had substantially greater rates of treatment completion and mean time remaining in treatment. Nevertheless, there was a tendency for the contingent group to have the lowest rate of opioid-positive urine samples. The study by Carroll et al. (1407) also found voucher incentives enhanced naltrexone adherence, which in turn was associated with less illicit opioid use.

The legal system can also provide an external motivation for adherence with naltrexone treatment. A random assignment study of 51 individuals on federal probation compared probation plus naltrexone and counseling with probation and counseling alone (1375). At the end of the 6-month study, no significant differences in treatment retention were found between the two groups, but the group that also received naltrexone had significantly lower rates of opioid-positive urine samples and reincarceration. Other studies of individuals with high levels of motivation to remain abstinent, such as business executives and physicians (1374), provide further evidence that this medication can be useful under the proper clinical circumstances.

(2) Safety and side effects of naltrexone

In general, naltrexone is a safe medication with few side effects. There has been concern that naltrexone can produce elevations in liver function tests, but these effects were observed in only four studies where patients were treated for atypical indications (e.g., obesity, dementia) with naltrexone doses higher than those used for the treatment of opioid dependence (e.g., up to 300 mg/day). These elevations in liver function tests occurred only with the 300 mg/day dose of naltrexone, were seen in only 1 out of 40 (2.5%) subjects under age 40 years compared with 18.5% of individuals older than age 40, and resolved with naltrexone discontinuation (1374). However, there is one letter reporting that the risk of increased liver function tests may occur if naltrexone is taken with NSAIDs (1047). Although the approved label for naltrexone cautions about its potential effects on liver function tests, the likelihood that these hepatic effects will occur in patients treated within the usual dose range (50–150 mg/day) and without pre-existing liver disease is minimal.

c) Clonidine and other nonopioid medications used for the treatment of opioid withdrawal

Clonidine is an α_2-adrenergic agonist approved in the United States for the treatment of hypertension but not for the treatment of opioid withdrawal. Clonidine has been used as an aid in controlling opioid withdrawal symptoms; unlike methadone, LAAM, buprenorphine, and naltrexone, it is not used as a maintenance treatment agent.

A related medication is lofexidine, another α_2-adrenergic agonist approved for the treatment of opioid withdrawal in the United Kingdom but not currently available in the United

States. There is evidence that lofexidine can be as effective as clonidine in the treatment of opioid withdrawal and that it produces less hypotension than does clonidine (1780–1782). However, at least one controlled inpatient study did not show that lofexidine markedly attenuated opioid withdrawal symptoms that were produced by a naloxone challenge (1783), and another study found buprenorphine was more effective than lofexidine when used in the treatment of opioid withdrawal (1784). The remainder of this section focuses on clonidine; no further review of lofexidine is provided here.

(1) Use of clonidine as a withdrawal (detoxification) agent

Several early studies tested the efficacy of clonidine when used on an inpatient basis for the treatment of opioid withdrawal (1388, 1785–1787). For example, a study that sought to determine optimal clonidine dosing parameters used a 2-week inpatient design and enrolled 25 methadone-maintained male and female patients (1380). Subjects had a double-blind abrupt discontinuation of their methadone dose and then started receiving thrice-daily clonidine 24 or 48 hours later, with flexible dosing based on signs and symptoms of withdrawal. Clonidine was found to reduce opioid withdrawal symptoms (compared with patient perception of previous withdrawal attempts), although symptoms of anxiety, restlessness, insomnia, and muscle aches were not relieved completely.

Another inpatient study used a classic substitution design to test the efficacy of acute doses of clonidine to suppress spontaneous opioid withdrawal symptoms in 10 male patients maintained on daily subcutaneous doses of morphine (1383). In this study, clonidine was found to be more effective than morphine in suppressing opioid withdrawal signs, although it was less effective than morphine in attenuating subjective complaints of opioid withdrawal.

Finally, a double-blind study from Spain compared the inpatient use of clonidine to a relatively low dose of methadone for short-term (8- to 10-day) withdrawal from heroin (1382). There were initially 45 subjects in the study; most of those who left the study early were taking clonidine. For those who remained (N=30), clonidine and methadone were found to be equally effective on measures of withdrawal. In an interesting finding, it appears that there was actually less residual opioid withdrawal at the end of this inpatient study for the clonidine patients compared with the methadone patients. However, the relatively short period of treatment and the low dose of methadone may have contributed to the finding of comparable efficacy for the two medications among patients who remained in the study.

Clonidine has also been examined for its efficacy in the outpatient treatment of opioid withdrawal (1384–1386). For example, a double-blind outpatient study with 49 opioid-dependent male and female participants compared methadone and clonidine in the treatment of withdrawal (1381). Participants in the study had relatively low levels of physical dependence (20 mg of daily methadone). In the study, participants underwent a double-blind 20-day methadone withdrawal or a 15-day clonidine withdrawal. There was no difference in the two groups among those successfully completing the withdrawal, although the clonidine-treated subjects tended to have greater withdrawal symptoms and to drop out earlier compared with the methadone-treated patients.

(2) Safety and side effects of clonidine

The most significant side effect associated with the use of clonidine in the treatment of opioid withdrawal is hypotension; the lowering of blood pressure by clonidine can be clinically significant for some opioid-dependent patients. This effect has been noted in many of the clinical studies of clonidine (1380, 1382, 1383, 1392, 1742, 1787) and has led to the common recommendation that when clonidine is used for opioid withdrawal, the treating physician regularly check the patient's blood pressure and hold the dose if hypotensive effects are noted.

Other side effects noted with clonidine when used for the treatment of opioid withdrawal have included sedation and other sleep difficulties, dry mouth, and constipation. In some cases,

it can be difficult to know if these more uncommon symptoms are side effects of clonidine or opioid withdrawal effects that are not fully treated by clonidine.

2. Psychosocial treatments

As noted previously, psychosocial treatments for opioid-related disorders have been studied only in programs that also provide maintenance treatment with either opioid agonists (e.g., methadone) or antagonists.

a) Cognitive-behavioral therapies

Woody et al. (177, 531, 1400, 1401) randomly assigned methadone maintenance patients to one of three groups: 1) drug counseling alone, 2) drug counseling plus supportive-expressive psychotherapy, or 3) drug counseling plus CBT. Outcomes were determined at 7 and 12 months. In patients with a moderate to high degree of depression or other psychiatric symptoms, drug counseling with supportive-expressive therapy or CBT was much more effective than drug counseling alone; for patients with low levels of psychiatric symptoms, all three treatment conditions were equally effective. These findings were essentially replicated in three community-based methadone maintenance clinics (218). O'Neill et al. (1402) evaluated a CBT intervention added to a methadone program for pregnant, injecting drug users at risk for HIV infection. CBT resulted in significantly greater reductions in HIV risk behaviors.

(1) Relapse prevention strategies

McAuliffe (1403) reported that when combined with participation in a self-help group, group relapse prevention based on a conditioning model of addiction was more effective than no treatment in reducing opioid use, unemployment, and criminal activities in recently detoxified patients.

b) Behavioral therapies

(1) Contingency management

In a study evaluating the intensity of behavioral treatments for methadone patients, McLellan et al. (170) determined whether the addition of contingency-based counseling, general medical care, and psychosocial services improved the efficacy of methadone maintenance treatment in a study of newly admitted opioid patients randomly assigned to three levels of care. Patients who received counseling and contingencies based on urine test results, in addition to methadone, had better drug use outcomes than those who received methadone only. Patients who in addition received on-site general medical and psychiatric care, employment services, and family therapy had the best outcomes of all three conditions. Methadone alone was an effective treatment for only a small percentage of patients.

Several studies have evaluated the use of contingency management in reducing the use of illicit drugs in opioid-dependent individuals who are maintained on methadone. In these studies, a reinforcer (reward) is provided to patients who demonstrate specified target behaviors such as providing drug-free urine specimens, accomplishing specific treatment goals, or attending treatment sessions. For example, offering methadone take-home privileges contingent on reduced drug use is an approach that capitalizes on an inexpensive reinforcer that is potentially available in all methadone maintenance programs. Stitzer and colleagues (197–199) have done extensive work in evaluating methadone take-home privileges as a reward for decreased illicit drug use. In a series of well-controlled trials, these researchers have demonstrated 1) the relative benefits of positive (e.g., rewarding desired behaviors such as abstinence) compared with negative (e.g., punishing undesired behaviors such as continued drug use through discharges or dose reductions) contingencies (197), 2) the attractiveness of take-home privileges over other incentives

available within methadone maintenance clinics (198), and 3) the relative effectiveness of rewarding drug-free urine specimens compared with other target behaviors (202).

Silverman and colleagues (195, 1295), drawing on the compelling work of Higgins and colleagues (described below), evaluated in a series of studies the efficacy of a voucher-based contingency management system to address concurrent illicit drug use (typically cocaine) among methadone-maintained opioid-dependent individuals. In this approach, urine specimens were required three times a week to systematically detect all episodes of drug use. Abstinence, verified through urine screens, was reinforced through a voucher system in which patients received points redeemable for items consistent with a drug-free lifestyle that were intended to help the patient develop alternate reinforcers to drug use (e.g., movie tickets, sporting goods). Silverman and colleagues (195, 1295) demonstrated the efficacy of this approach in reducing illicit opioid and cocaine use.

Opioid antagonist treatment (naltrexone) offers many advantages over methadone maintenance, including the fact that it is nonaddicting and can be prescribed without concerns about diversion, has a benign side effect profile, and can be less costly in terms of demands on professional time and patient time than the daily or near-daily clinic visits required for methadone maintenance (165). Most important are the behavioral aspects of treatment, as unreinforced opiate use allows the extinction of the association between cues and drug use. Although naltrexone treatment is likely to be attractive only to a small number of opioid-dependent individuals (166), naltrexone's unique properties make it an important alternative to methadone maintenance and other agonist approaches.

However, despite its many advantages, naltrexone has not fulfilled its promise. Naltrexone treatment programs remain comparatively rare and underutilized as compared with methadone maintenance programs (165), largely because of problems with retention, particularly during the induction phase; an average of 40% of patients drop out during the first month of treatment and 60% drop out by 3 months (166). In the 1970s, several preliminary evaluations identified the promise of using behavioral interventions to address naltrexone's weaknesses, including providing incentives for adherence with naltrexone treatment (1404, 1405) and the addition of family therapy to naltrexone treatment (1788). However, the interventions were not widely adopted, adherence remained a major problem, and naltrexone treatment and research dropped off considerably until the past few years, when the need for alternatives to methadone maintenance stimulated a modest revival of interest in naltrexone.

Some of the most recent promising data about strategies to enhance retention and outcome in naltrexone treatment have come from investigations of contingency management approaches. Preston et al. (1406) found improved retention and naltrexone treatment adherence with an approach that provided vouchers for adherence as compared with standard naltrexone treatment that did not provide vouchers. Carroll and colleagues (167, 1407) found that reinforcement of naltrexone treatment adherence and drug-free urine specimens, alone or in combination with family involvement in treatment, improved retention rates and reduced drug use among recently detoxified opioid-dependent individuals.

(2) Cue exposure treatment

Cue exposure treatment has been demonstrated to be effective in reducing classically conditioned responses to substance-related cues in a small group of patients with opioid use disorders (189).

c) Psychodynamic and interpersonal therapies

The effectiveness of adding a psychodynamic therapy to a program of methadone maintenance has been investigated. Woody et al. (177, 218) found that supportive-expressive therapy was more effective than drug counseling alone for patients with high levels of other psychiatric symptoms. Rounsaville et al. (1789) attempted to compare the efficacy of a 6-month course of weekly individual IPT with a low-contact comparison condition for individuals in a full-service meth-

adone maintenance program that included weekly group psychotherapy. Patients with opioid dependence who met the inclusion criteria (including the presence of an additional nonpsychotic psychiatric diagnosis) were randomly assigned to the two groups. However, only 5% of the eligible patients agreed to participate (compared with 60% in the Woody et al. study), and only about 50% completed the trial. The highly selective nature of the participants (i.e., 95% of eligible patients refused), the high attrition rate, and the lack of significant outcome differences between the two groups led to the conclusions that it is very difficult to engage opioid-dependent patients in individual IPT and that the potential benefit of such treatment is unclear for those who do participate.

Psychodynamically oriented group therapy modified for substance-dependent patients appears to be effective in promoting abstinence when combined with behavioral monitoring and individual supportive psychotherapy (1301).

Although some follow-up studies of naturalistic treatment have found equivalent efficacy for methadone maintenance and outpatient drug-free programs for heroin users (61, 1396–1398), early attempts at providing psychotherapy alone have yielded unacceptably high attrition rates (1399).

PART C
FUTURE RESEARCH NEEDS

Despite the significant amount already known about substance use disorders, our understanding of these disorders as well as the treatment of patients would be improved by research focusing on a number of areas. One broad area involves delineating the multiple factors that alter the development, manifestations, clinical course, and prognosis of substance use disorders. Such factors may include developmental, biological, cognitive, and sociocultural factors, as well as the impact of early experiences with substances of abuse and the effects of co-occurring psychiatric or general medical conditions. Given the significant numbers of individuals with a co-occurring psychiatric and substance use disorder, improved methods for diagnosis are needed, including approaches for defining the precise temporal and etiological relation between substance use and other forms of psychopathology. Enhanced approaches for identifying prescription opioid dependence would also be beneficial, particularly in individuals with underlying physical disorders that are associated with significant pain.

Research on the modifying factors and underlying causes of substance use disorders is inextricably linked to a need for studies of the gene or genes that influence the heritability of abuse and dependence on specific substances (e.g., alcohol, opioids) as well as the heritability of substance use disorders in general. Genetic factors may also augment risk for or exert protective influences on the development and manifestations of substance use disorders. In a similar vein, other research approaches, including epidemiological studies, can assist in identifying risk and protective factors that influence vulnerability to substance use disorders.

Another topic that requires further research relates to the acute and chronic effects of abused substances. This includes the effects of substances on a variety of organ systems as well as the pathogenesis of substance-induced fetal abnormalities after in utero exposure to substances of abuse. In the CNS, the acute effects of substances on brain morphology, biochemistry, and physiology may be revealed through brain imaging or other assessment techniques. The time course of recovery from these effects once a patient is free of substances also needs delineating.

Such studies may complement assessments of the biological, cognitive, and behavioral factors contributing to the development of prolonged abstinence syndromes in patients previously dependent on nicotine, alcohol, marijuana, cocaine, or opioids.

Virtually every aspect of substance use disorder treatment provides an opportunity for further study and improvements in clinical care. More information is needed about the selection of treatment settings according to the unique needs of the individual patient. The utility of a particular treatment setting for specific disorders may also be worthy of further study (e.g., inpatient approach to smoking cessation). Treatment programs may exhibit differential efficacies or cost-effectiveness depending on the site of treatment, the mix of specific treatment modalities used, the organizational and managerial aspects of the treatment program, and the specific population of patients being served (e.g., individuals using more than one substance or having a co-occurring psychiatric disorder, at-risk individuals receiving preventive services or early interventions).

In addition to learning about specific treatment settings, more information is needed on the specific treatments for intoxication and withdrawal. Even in the treatment of alcohol withdrawal, for which there is considerable evidence and consensus, questions remain about the most effective class(es) of agents, the most effective agent(s) within a particular class, the most effective dosing regimen(s), and the choice of specific agents for treating specific patient subgroups or specific symptoms of withdrawal. For all substance use disorders, research should delineate the intensity and staging of treatment (i.e., using different treatments in different settings at different phases of the disorder) and the interactive (i.e., additive, synergistic, or antagonistic) effects of various treatment modalities when applied concurrently or in sequence. Such studies of treatment modalities, including those in current use and those being developed, will need to examine short-, intermediate-, and long-term outcomes in specific patient populations. The impact of sociodemographic, psychiatric, and general medical characteristics and patient treatment preferences on treatment adherence and outcome are also relevant.

In terms of pharmacotherapeutic approaches to treatment, the development of new therapies might focus on effectively decreasing symptoms of withdrawal (e.g., use of delta-9 tetrahydrocannabinol in marijuana dependence, nonopioid agents for opioid dependence), reducing short- and long-term craving in active and abstinent substance users (e.g., mixed agonist/antagonists for opioid dependence, novel agents including vaccines for cocaine dependence), treating dependence (e.g., to marijuana, cocaine, prescription opioids), and reversing the physiological effects of chronic substance use on the functioning of the brain and other affected organs. For pregnant substance-abusing women, it will be important to develop new pharmacotherapies that do not affect the fetus. In terms of existing pharmacotherapies, additional studies are needed on using combinations of pharmacotherapies (e.g., use of multiple NRTs or NRT and bupropion for nicotine dependence) as well as on the effects of specific pharmacotherapies in treating patients with co-occurring psychiatric and substance use disorders. Additional studies may help guide the identification of patient populations that will benefit from specific treatments (e.g., characteristics of patients who would benefit from naltrexone versus acamprosate for the treatment of an alcohol use disorder). Other therapeutic options could be developed depending on the gene or genes involved in the etiology or treatment responsiveness of substance use disorders (e.g., gene therapy, pharmacogenetics approach to optimizing the choice of pharmacotherapy).

Equally essential is additional research on psychosocial therapies for substance use disorders. Effective psychosocial interventions for the treatment of marijuana dependence are particularly important given the limited options for addressing this problem at present. However, the study of a broad range of psychosocial therapies will enhance therapeutic options for each substance use disorder. For children, adolescents, and adults at risk for a substance use disorder, research is needed on the long-term efficacy of behavioral, psychosocial, and family-based interventions. Other specific subgroups of patients (e.g., those with prescription opioid dependence, those with a co-occurring psychiatric and substance use disorder, individuals with treatment-resistant disorders) may require modified approaches to treatment. For individuals with multiple disor-

ders, integrated approaches to treatment are likely to be needed. Combinations of psychosocial and pharmacological therapies should be examined in terms of augmenting short-term, immediate, and long-term patient outcomes. With each of the psychosocial therapies, research should determine the impact of sociodemographic, psychiatric, and general medical characteristics and patient treatment preferences on treatment participation and outcome.

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American Academy of Addiction Psychiatry
American Academy of Child and Adolescent Psychiatry
American Academy of Clinical Psychiatrists
American Academy of Pediatrics
American Academy of Psychiatry and the Law
American Association of Oriental Medicine
American Group Psychotherapy Association
American Mental Health Counselors Association
American Music Therapy Association
American Psychological Association
American Society of Addiction Medicine
Association for Academic Psychiatry
Association for Cognitive and Behavioral Therapies
Association for Medical Education and Research on Substance Abuse
Group for the Advancement of Psychiatry
Managed Health Network, Inc.
National Acupuncture and Oriental Medicine Alliance
National Association of Social Workers
Royal College of Psychiatrists
Society for Adolescent Medicine
Texas Society of Psychiatric Physicians
World Federation for Mental Health

REFERENCES

The following coding system is used to indicate the nature of the supporting evidence in the summary recommendations and references:

[A] *Double-blind, randomized clinical trial.* A study of an intervention in which subjects are prospectively followed over time; there are treatment and control groups; subjects are randomly assigned to the two groups; both the subjects and the investigators are blind to the assignments.

[A–] *Randomized clinical trial.* Same as above but not double-blind.

[B] *Clinical trial.* A prospective study in which an intervention is made and the results of that intervention are tracked longitudinally; study does not meet standards for a randomized clinical trial.

[C] *Cohort or longitudinal study.* A study in which subjects are prospectively followed over time without any specific intervention.

[D] *Case-control study.* A study in which a group of patients is identified in the present and information about them is pursued retrospectively or backward in time.

[E] *Review with secondary data analysis.* A structured analytic review of existing data, e.g., a meta-analysis or a decision analysis.

[F] *Review.* A qualitative review and discussion of previously published literature without a quantitative synthesis of the data.

[G] *Other.* Textbooks, expert opinion, case reports, and other reports not included above.

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