Medication-Assisted Treatment
For Opioid Addiction in Opioid Treatment Programs

A Treatment Improvement Protocol

TIP 43

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Substance Abuse and Mental Health Services Administration
Center for Substance Abuse Treatment
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MEDICATION-ASSISTED TREATMENT

12 Treatment of Co-Occurring Disorders

In This Chapter...

Many people who are opioid addicted have co-occurring mental disorders. However, mental health and addiction treatment systems often are separated. This situation may result in patients' being treated at one location for addiction and at another for mental disorders. Some mental health care facilities do not accept patients in medication-assisted treatment for opioid addiction (MAT), forcing these patients to choose which disorder to treat. These problems, along with uncertainties about effective interventions for patients with both addiction and mental disorders, have stimulated research in this area. This chapter summarizes current thinking and consensus panel recommendations on screening, diagnosing, and treating these patients in opioid treatment programs (OTPs).

The term "co-occurring disorder" in this TIP means a mental disorder that coexists with at least one substance use disorder in an individual. The consensus panel acknowledges that other types of disorders also occur with substance use disorders, such as cognitive and medical disorders and physical disabilities. These conditions also require individualized treatment approaches, and, for patients who are opioid addicted, other chapters in this TIP present discussions of treatments for other types of disorders that occur with substance use disorders. Chapter 6 discusses patients with physical disabilities. Chapter 8 discusses patients with cognitive disorders. Chapter 10 discusses patients with other medical disorders.

TIP 42, *Substance Abuse Treatment for Persons With Co-Occurring Disorders* (CSAT 2005*b*); *Report to Congress on the Prevention and Treatment of Co-Occurring Substance Abuse Disorders and Mental Disorders* (Substance Abuse and Mental Health Services Administration 2002*c*); and *Strategies for Developing Treatment Programs for People With Co-Occurring Substance Abuse and Mental Disorders* (Substance Abuse and Mental Health Services Administration 2003*d*) provide additional information on co-occurring disorders in substance abuse treatment. This chapter focuses on co-occurring disorders in patients with opioid addiction.

Patients in MAT who have co-occurring disorders often exhibit behaviors or feelings that interfere with treatment. These symptoms may indicate either underlying co-occurring disorders that would be present regardless of substance use (i.e., independent or primary disorders) or co-occurring disorders caused by substance use (i.e., substance-induced or secondary disorders). Symptoms may also indicate the presence of both independent disorders and self-induced disorders along with substance use disorders. Patients may have identifiable co-occurring disorders on admission to an OTP, or disorders may emerge during MAT.

Unless MAT providers distinguish co-occurring disorders accurately by type and address them appropriately, these disorders likely will complicate patients' recovery and reduce their quality of life. Numerous studies have indicated that rapid, accurate identification of patients' co-occurring disorders and immediate interventions with appropriate combinations of psychiatric and substance addiction therapies improve MAT outcomes. The consensus panel for this TIP endorses this view. Many standard treatments for mental disorders can be modified readily for patients with co-occurring disorders in MAT.

Prevalence of Co-Occurring Disorders

Exhibit 12-1 lists the most common co-occurring disorders among patients in MAT, based on representative studies (e.g., Brooner et al. 1997; Mason et al. 1998). They are grouped into Axis I and II disorders, as defined in *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (DSM-IV-TR) (American Psychiatric Association 2000).

Studies comparing patients in MAT with the general population have confirmed higher rates of co-occurring Axis I and II disorders in these patients (e.g., Calsyn et al. 1996; Mason et al. 1998). In a study by Brooner and colleagues (1997), nearly half of patients in MAT had co-occurring disorders during their lifetimes.

Factors Affecting Prevalence of Co-Occurring Disorders

Some factors found to increase the prevalence of co-occurring disorders among people with substance use disorders include older age, lower socioeconomic status, and residence in urban areas (Kessler et al. 1994); homelessness (North et al. 2001); and incarceration (Robins et al. 1991). Certain mental disorders (e.g., antisocial personality disorder [APD], schizophrenia) and some affective and anxiety disorders (phobias, bipolar depression) have been found to be more prevalent among persons with substance use disorders than in the general population (Regier et al. 1990). However, some of these studies did not determine whether symptoms of co-occurring disorders were related to the pharmacological effects of substances or to an underlying non–substance-related disorder. TIP 42, *Substance Abuse Treatment for Persons With Co-Occurring Disorders* (CSAT 2005*b*), discusses factors affecting the prevalence of co-occurring disorders.

Gender Differences in Prevalence of Co-Occurring Disorders

Rates of co-occurring disorders have been found to differ between men and women. For example, Ward and colleagues (1998*b*) found that more women than men who were opioid addicted had affective and anxiety disorders, whereas more men than women who were opioid addicted had APD and were dependent on alcohol. A study by Brooner and colleagues (1997) found women were more likely than men to have Axis I diagnoses, particularly major depression; seven times more likely to have borderline personality disorders; only half as likely to be diagnosed with APD; and less likely than men to manifest problems with other

Exhibit 12-1

Common Co-Occurring Disorders in Patients Who Are Opioid Addicted

Axis I Categories (Clinical Disorders and Other Conditions)	Axis II Categories (Personality Disorders and Mental Retardation)
• **Mood Disorders** Major depressive disorder Dysthymic disorder Bipolar disorder	• **Personality Disorders** APD Borderline personality disorder Narcissistic personality disorder
• **Anxiety Disorders** Generalized anxiety disorder Posttraumatic stress disorder (PTSD) Social phobia Obsessive-compulsive disorder Panic disorders • **Attention Deficit/Hyperactivity Disorder (AD/HD)** • **Schizophrenia and Other Psychotic Disorders** • **Cognitive Disorders** • **Eating Disorders** • **Impulse Control Disorders: Pathological Gambling** • **Sleep Disorders**	

substances, including alcohol. Another study indicated that female patients receiving methadone were more likely than male patients to have psychotic and affective disorders (Calsyn et al. 1996). Another study of patients in MAT found that women were more likely than men to have PTSD (Villagomez et al. 1995).

Motivation for Treatment and Co-Occurring Disorders

Some studies have found that co-occurring disorders motivated people who were addicted to seek treatment. Community surveys from both the Epidemiologic Catchment Area study and the National Comorbidity Study found that, among respondents with substance use disorders, those with co-occurring disorders were more likely to obtain treatment (Kessler et al. 1994, 1996; Regier et al. 1990).

Etiology of Co-Occurring Disorders

Mueser and colleagues (1998) identified four common models to explain the relationship between co-occurring and substance use disorders:

- **Primary substance use disorder and secondary co-occurring disorder.** This "disease model" holds that substance use disorders cause most co-occurring disorders in patients. Appropriate treatment, by this theory, focuses on the underlying substance use.
- **Primary co-occurring disorder and secondary substance use disorder.** This "self-medication" model, proposed by Khantzian (1985), argues that preexisting mental disorders are a significant cause of substance use disorders. People who are drug addicted choose drugs that lessen painful feelings caused by their mental disorders, for example, opioids or alcohol to alleviate anxiety or cocaine or other stimulants to relieve depression. By extension of this view, adequate treatment of the psychopathology resolves the substance use disorder.
- **Common pathway.** This model holds that shared genetic or environmental factors may cause both substance use and co-occurring disorders. For example, accumulating evidence indicates that childhood conduct disorders that persist to become adult antisocial or borderline personality disorders are significant risk factors for substance abuse (e.g., Compton et al. 2000; Mueser et al. 1999). Other studies (e.g., Ahmed et al. 1999; Nunes et al. 1998*b*) have found that relatives of patients who were opioid addicted had higher rates of major depression, alcoholism, and substance use disorders, indicating that genetic factors increase susceptibility to both addiction and co-occurring disorders.

[A]dmission and ongoing assessment routinely should incorporate screening for co-occurring disorders.

- **Bidirectional model.** This model emphasizes that socioenvironmental and interpersonal factors, such as poverty, social isolation, drug availability, or lack of accountability by adult caregivers, also contribute to both substance use and co-occurring disorders through a complex interaction between environment and genetic susceptibility. The bidirectional model has not been evaluated systematically.

Screening for Co-Occurring Disorders

The consensus panel believes that admission and ongoing assessment routinely should incorporate screening for co-occurring disorders. This screening should yield a simple positive or negative result, depending on whether signs or symptoms of co-occurring disorders exist. A negative result generally should rule out immediate action, and a positive result should trigger detailed assessment by a trained professional (see chapter 4).

To identify patients in MAT with co-occurring disorders, treatment providers must decide

- When and how to screen patients
- How to integrate psychological screening with standard intake assessment
- Which instruments to use for screening and confirming co-occurring disorders
- What qualifications are needed by staff who conduct screenings
- How to classify symptoms and other evidence
- How to determine the most appropriate treatment methodology and level of care.

Specific Screening Procedures

OTPs should establish specific screening procedures for co-occurring disorders and train counselors and intake workers to perform these procedures, including how to recognize the presenting symptoms of the most commonly encountered co-occurring disorders. Few significant differences in symptoms of mental disorders exist between patients who are addicted to opioids and other people who are not; therefore, the symptoms described in

DSM-IV-TR are applicable during admission screening. When possible, screening for co-occurring disorders should be linked with other assessments to avoid duplicate efforts by staff and unnecessary burdens on patients' time. An OTP's screening procedures for co-occurring disorders should specify

- Questions or instruments to be used
- When and where to conduct screening segments (e.g., address all safety-related questions during initial intake and defer other questions until applicants are no longer intoxicated or in withdrawal—but wait no longer than a specified period after admission)
- Who conducts screenings
- How to record results
- Cutoff scores or other indicators of positive results for co-occurring disorders
- Exactly how to handle positive results (e.g., whom to inform, how, and when; what constitutes a psychiatric emergency and how to address it)
- How extensively a patient's self-reported information must be corroborated with information from other sources (e.g., family and friends, caseworkers, previous treatment records)
- Which staff members to consult if questions arise about these procedures or the results.

Screening for co-occurring disorders usually entails determining

- An applicant's immediate safety and self-control, including any suicide risk, aggression or violence toward others, or domestic or other abuse or victimization and the ability to care for himself or herself (see "Handling Emergency Situations" below).
- Previous diagnosis, treatment, or hospitalization for a mental disorder and, if applicable, why, when, and where, as well as the treatment received and its outcome. Questions about the relationship of mental disorders to substance use—for example, whether a mental disorder was present during abstinence or before the substance use disorder—determine whether a co-occurring disorder is substance induced or independent.
- The applicant's current co-occurring disorder symptomatology based on DSM-IV-TR criteria, including whether any psychotropic medications have been prescribed or are being used (usually included on a screening questionnaire).
- Trauma history (e.g., physical or sexual abuse, living through a natural disaster or war, witnessing death or tragedy). Questions about trauma should be brief and general, without evoking details that might precipitate stress. Several screening instruments for PTSD are described in other TIPs (see the forthcoming TIP *Substance Abuse and Trauma* [CSAT forthcoming *d*]; TIP 25, *Substance Abuse Treatment and Domestic Violence* [CSAT 1997*b*]; and the Modified PTSD Symptom Scale: Self-Report in TIP 36, *Substance Abuse Treatment for Persons With Child Abuse and Neglect Issues* [CSAT 2000*d*]).
- Any history of mental disorder-related symptoms among immediate relatives and their diagnoses, treatments, or hospitalization.
- Any unusual aspects of an applicant's appearance, behavior, and cognition. If indications of a cognitive impairment are present, a mental status examination should be conducted.

Screening for cognitive impairment

The accuracy of instruments to screen for co-occurring disorders may be compromised if administered to patients with cognitive impairments. A brief preexamination of cognitive functioning during a mental status examination is recommended for individuals who are disoriented with respect to time, place, or person; have memory problems; or have difficulty understanding information in their first language. TIP 29, *Substance Use Disorder Treatment for People With Physical and Cognitive Disabilities* (CSAT 1998*c*), contains an 18-item screening instrument for cognitive

impairment and functional limitations. TIP 33, *Treatment for Stimulant Use Disorders* (CSAT 1999*c*), lists nine brief screening tools to determine cognitive impairment and reproduces the Repeated Memory Test. Treatment providers who prefer the familiar Mini-Mental State Examination (Folstein et al. 1975) can order either the standard or extended version via the World Wide Web at www.minimental.com.

Screening Tools

Many States require specific screening or assessment instruments, such as the Addiction Severity Index (ASI), to document baseline patient data. Other important considerations in selecting a screening tool for co-occurring disorders include its psychometric properties and cultural appropriateness and, if the test is self-administered, the literacy level required. The consensus panel believes that no instrument in an OTP can identify co-occurring disorders satisfactorily, and many of the most thoroughly tested are not in the public domain. The ASI records symptoms of mental disorders but does not diagnose. More information on the ASI and other screening instruments, including Mental Health Screening Form III, the Mini International Neuropsychiatric Interview (M.I.N.I.), and some proprietary instruments, is in TIP 42, *Substance Abuse Treatment for Persons With Co-Occurring Disorders* (CSAT 2005*b*). Other tools focusing on particular disorders or pathologies (e.g., suicide danger, PTSD, AD/HD, depression) can be accessed through the Web sites listed in Appendix 12-A.

Making and Confirming a Psychiatric Diagnosis

After a possible co-occurring disorder is identified during screening, an experienced, licensed mental health clinician (e.g., psychiatrist, psychologist, clinical social worker) should perform additional evaluation to make or confirm a diagnosis. Ideally, this expertise is available at the OTP. When it is not, appropriate consultants and referral resources must be substituted, but procedures to use and reimburse these resources should be well established.

The most widely used systems to classify mental and substance use disorders are provided in DSM-IV-TR and the *International Classification of Diseases, 10th Edition* (ICD-10), *Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines* (World Health Organization 1992). Both systems present diagnosis criteria accepted by national (DSM-IV-TR) or international (ICD-10) experts.

DSM-IV-TR Criteria

Although many insurance companies require International Classification of Diseases diagnostic codes for reimbursement purposes, clinicians and researchers in the United States traditionally use the DSM classification system. As this system has evolved over several editions, its authors have made important changes in definitions for substance-related disorders. Specifically, the DSM-IV-TR divides these disorders into two types: substance use disorders and substance-induced co-occurring disorders.

Substance use disorders

DSM-IV-TR divides substance use disorders into abuse and dependence with or without physiological features such as tolerance or withdrawal. It also makes distinctions pertaining to early or sustained remission; programs offering agonist, partial agonist, or agonist/antagonist therapy; and treatment while living in a controlled environment (e.g., jail).

Substance-induced co-occurring disorders

Substance-induced co-occurring disorders are associated with intoxication, withdrawal, and the persistent effects of substances of abuse. Substance-induced *persisting* disorders are those in which substance-related symptoms continue long after a person stops using a drug (e.g., prolonged flashbacks from hallucinogen use, substance-induced persistent dementia,

substance-induced persistent amnesia). Exhibit 12-2 shows the association between substance-induced co-occurring disorders and substances of abuse. It is noteworthy that different drugs have been associated with different types of co-occurring disorders and that some (such as opioids) have relatively few or no reported psychotoxic effects, whereas others have many.

Structured and Semistructured Interview Formats for Psychiatric Diagnoses

A number of carefully designed and tested instruments are available to determine DSM-IV or ICD-10 diagnoses, although a careful clinical interview usually can serve this purpose. Not all instruments have been updated for DSM-IV-TR diagnoses, but DSM-IV diagnoses are similar. Examples include the

- Structured Clinical Interview for DSM-IV Axis I and II Disorders, Clinical Versions
- Composite International Diagnostic Interview, Core Version 2.1
- Psychiatric Research Interview for Substance Abuse and Mental Health Disorders
- Diagnostic Interview Schedule, Version 4
- Alcohol Use Disorder and Associated Disabilities Interview Schedule.

TIP 42, *Substance Abuse Treatment for Persons With Co-Occurring Disorders* (CSAT 2005*b*), discusses these and other screening and assessment instruments and their sources at greater length.

Differential diagnosis

Careful assessment including a family history is critical to determine whether presenting symptoms indicate independent co-occurring disorders or disorders induced by substance use or a general medical or neurological condition. In many cases, people who abuse multiple substances have both an independent co-occurring disorder and various substance-induced symptoms precipitated by intoxication or withdrawal. Substance use can magnify symptoms of independent co-occurring disorders. For example, substance use can heighten the mood swings of bipolar disorder; intensify the hallucinations and paranoid delusions of schizophrenia; or increase the risk of suicide, violence, and impulsive behaviors among individuals with antisocial or borderline personality disorders (American Psychiatric Association 2000).

> [I]ndependent and substance-induced co-occurring disorders differ in their course.

The accuracy of differential diagnosis has treatment implications because independent and substance-induced co-occurring disorders differ in their course. Independent disorders tend to follow a typical course for each diagnosis and require specific, long-term treatment (e.g., pharmacotherapy, psychotherapy). Substance-induced disorders tend to follow the course of the substance use disorder and to dissipate with abstinence, although persistent disorders can deviate from this sequence. Substance-induced symptoms can be disruptive at the start of MAT, but they typically do not require ongoing psychiatric treatment (Woody et al. 1995*a*).

Timing for confirming a diagnosis

Accurate diagnosis of independent co-occurring disorders is difficult during the early phases of MAT because substance-induced symptoms also usually are present. A definitive diagnosis often must wait until a patient is stabilized on treatment medication for a minimum of 5 to 7 days (but preferably 2 to 4 weeks) and any continuing substance use is eliminated. Although several weeks of abstinence may improve the accuracy of diagnoses, symptoms of severe co-occurring disorders (e.g., suicidality, psychotic reaction) need prompt attention and might require more immediate pharmacological

Exhibit 12-2

DSM-IV-TR Classification of Diagnoses Associated With Different Classes of Substances

	Dependence	Abuse	Intoxication	Withdrawal	Intoxication Delirium	Withdrawal Delirium	Dementia	Amnestic Disorder	Psychotic Disorders	Mood Disorders	Anxiety Disorders	Sexual Dysfunctions	Sleep Disorders
Alcohol	X	X	X	X	I	W	P	P	I/W	I/W	I/W	I	I/W
Amphetamines	X	X	X	X	I				I	I/W	I	I	I/W
Caffeine			X								I		I
Cannabis	X	X	X	X	I				I		I		
Cocaine	X	X	X	X	I				I	I/W	I/W	I	I/W
Hallucinogens	X	X	X		I				I*	I	I		
Inhalants	X	X	X		I		P		I	I	I		
Nicotine	X			X									
Opioids	X	X	X	X	I				I	I		I	I/W
Phencyclidine	X	X	X		I				I	I	I		
Sedatives, hypnotics, or anxiolytics	X	X	X	X	I	W	P	P	I/W	I/W	W	I	I/W
Polysubstance	X												
Other	X	X	X	X	I	W	P	P	I/W	I/W	I/W	I	I/W

*Also Hallucinogen Persisting Perception Disorder (flashbacks).
Note: X, I, W, I/W, or P indicates that the category is recognized in DSM-IV-TR. In addition, I indicates that the specifier With Onset During Intoxication may be noted for the category; W indicates that the specifier With Onset During Withdrawal may be noted for the category (except for Withdrawal Delirium); and I/W indicates that either With Onset During Intoxication or With Onset During Withdrawal may be noted for the category. P indicates that the disorder is Persisting.

Source: Reprinted from DSM-IV-TR. Copyright 2000, American Psychiatric Association.

treatment or hospitalization (Woody et al. 1995*a*). OTPs should be aware that even symptoms of less severe co-occurring disorders can prevent a patient's stabilization and should be addressed quickly.

Guidelines for distinguishing non–substance-induced from substance-induced co-occurring disorders

To assist with a differential diagnosis, the following information (Woody et al. 1995*a*) should be collected and reviewed:

- Previous history of mental disorders and treatment, focusing on temporal relationship of symptoms to substance use and response to previous treatment
- Type, quantity and frequency, and time of last use of illicit substances or prescribed psychotropic drugs (each substance class produces specific physiological and behavioral effects, especially during acute intoxication or withdrawal after prolonged, high-dosage use)
- Family history of mental disorders.

DSM-IV-TR (American Psychiatric Association 2000) offers the following procedures to ascertain whether a co-occurring disorder is primary or secondary:

- Label the disorder according to predominant symptom pattern and specified criteria (e.g., mood, anxiety, psychotic disorder)
- Consider the co-occurring disorder *primary* (not substance induced) if
  - Symptoms developed before the substance use disorder
  - Symptoms have persisted during 30 days or more of abstinence (depending on the characteristic withdrawal course for each substance)
  - Symptoms are inconsistent with or exceed those produced by the abused substance at the dosage used (e.g., hallucinations after opioid withdrawal, paranoid delusions after low-dose marijuana use)
  - Substance use or another medical disorder cannot account better for the symptoms
- Consider the mental disorder *secondary* (substance induced) if
  - Symptoms developed only during periods of active substance use or within 1 month of intoxication or withdrawal
  - Symptoms are consistent with intoxication or withdrawal from substances used
  - Other features (e.g., age at onset) are atypical for primary co-occurring disorder
  - Another co-occurring or medical disorder does not account better for the symptoms.

Prognosis for Patients With Co-Occurring Disorders

Patients with co-occurring disorders generally have been found to have poorer prognoses and to be more difficult to treat than those with diagnoses of either a substance use or mental disorder (Dausey and Desai 2003; Kessler 1995). Research has suggested that persons with co-occurring disorders are at higher risk of suicide, psychiatric hospitalization, legal difficulties and incarceration, homelessness, life-threatening infectious diseases, domestic violence, abuse or neglect of their children, unemployment, and other interpersonal problems (e.g., Dausey and Desai 2003; Room 1998).

Effects of Co-Occurring Disorders on Treatment Outcomes

The conventional view, which has considerable empirical support, is that unidentified, untreated co-occurring disorders impede progress for patients in MAT and lead to difficulties in engaging patients in treatment, establishing a

therapeutic alliance between patients and treatment providers, maintaining adherence to treatment regimens, eliminating substance abuse and other risky behaviors, and preventing premature dropout or early relapse. Conversely, a review by Drake and Brunette (1998) concluded that substance abuse complicates co-occurring disorders, often precipitating relapse to psychopathological symptoms, hospitalization, disruptive behavior, familial problems, residential instability, decreased functional status, HIV infection, or medication noncompliance.

Because research on treatment outcomes for patients with opioid addiction and co-occurring disorders usually examines small groups of subjects and because patients in these groups are not homogeneous, the general applicability of current findings is limited. Many confounding factors exist (Room 1998). Despite these limitations, numerous studies have found that many patients with co-occurring disorders did well when appropriate psychiatric and substance abuse treatments were delivered. The consensus panel recommends more intensive and psychiatrically specific treatment for these patients.

Effects of Symptom Severity

Studies disagree on whether the severity of co-occurring disorder symptoms in patients who are addicted is a useful predictor of treatment outcomes. Early studies found that the severity of co-occurring disorder symptoms, particularly in patients with anxiety or depression, strongly predicted treatment outcomes and that the most severely symptomatic patients had the heaviest substance use and most impaired adjustment, whereas the least symptomatic did best in addiction treatment (McLellan et al. 1993; Rounsaville et al. 1986). However, later studies have found that higher symptom severity, although associated with higher levels of substance use and worse overall adjustment, did not predict treatment response. In one study, drug test results for patients with severe psychopathology improved significantly over time (Belding et al. 1998). In another study, patients in MAT for at least 90 days who had co-occurring disorders and high levels of symptom severity had positive treatment responses (Joe et al. 1995). Patients with more than one co-occurring disorder engaged in treatment more readily than those who were addicted only, and both groups were similar in average incidence of drug use or criminal activity. Patients with depression, anxiety, suicidal ideation, and other pathologies at intake were twice as likely to attend individual—but not group—counseling sessions and significantly more likely to discuss psychological problems than those reporting none of these symptoms.

Consequently, caution is advised in predicting a simple, stable correlation between symptom severity of co-occurring disorders and treatment outcomes. However, the consensus panel believes that co-occurring disorders can improve substantially but that outcomes depend heavily on additional treatment being provided for these disorders and that patients with severe symptoms may require longer, more intensive treatment.

Prognosis for Specific Co-Occurring Disorders

Effects of co-occurring APD on progress in MAT

APD has been estimated to affect 24 to 39 percent of people seeking treatment for opioid addiction (Brooner et al. 1997; Darke et al. 1996; King et al. 2001). Some studies have found that people with APD and opioid addiction had more criminal activity, more history of early violent and aggressive behaviors, greater likelihood of engaging in activities that risked HIV transmission, more extensive and severe polydrug abuse, and earlier onset of opioid use than persons who were opioid addicted without APD (Brooner et al. 1997; Darke et al. 1996).

However, agreement is lacking on the significance of a diagnosis of APD in MAT. Some studies have found that patients with

co-occurring APD had less favorable outcomes than those without this disorder, even if the former group received additional psychotherapy (e.g., Alterman et al. 1998; Galen et al. 2000). Others have found that patients with APD in MAT improved to the same extent, on average, as those without APD (e.g., Cacciola et al. 1995; Darke et al. 1996), although the former group had more severe symptoms at both entry and followup. This lack of consistent findings has led some researchers to question the clinical utility, reliability, or validity of DSM-IV-derived APD diagnoses in MAT patients (Alterman et al. 1998; Cacciola et al. 1995). Darke and colleagues (1998) expressed concern that people addicted to opioids might be diagnosed with APD as a reflection of their risk-taking and drug-dealing lifestyles rather than actual existence of their underlying personality disorders.

Patients with APD can improve in MAT, and OTPs should be prepared to manage and limit aggressive, impulsive, or criminal behaviors by patients, regardless of whether the behaviors are related to a DSM-based diagnosis of APD.

Effects of co-occurring PTSD on progress in MAT

Increasing attention has been paid to the high prevalence and negative effects of PTSD on patients in MAT, especially women (Villagomez et al. 1995). Hien and colleagues (2000) found that women with symptoms of PTSD at admission were significantly less likely than those without such symptoms to adhere to treatment requirements, including abstinence from substances during the first 3 months of MAT. In another study, patients with current PTSD symptoms had greater drug abuse severity (Clark et al. 2001). These patients may need special attention paid to depression and suicidal ideation (Villagomez et al. 1995). TIP 36, *Substance Abuse Treatment for Persons With Child Abuse and Neglect Issues* (CSAT 2000*d*), and TIP 42, *Substance Abuse Treatment for Persons With Co-Occurring Disorders* (CSAT 2005*b*), provide more information on PTSD and substance abuse treatment.

Effects of co-occurring AD/HD on progress in MAT

King and associates (1999) studied 125 people admitted to OTPs over a 1-year period to determine the relationship of AD/HD to current attention problems, other co-occurring and substance use disorders, and other outcome variables. Nineteen percent of patients had a history of AD/HD, and 88 percent with lifetime AD/HD diagnoses had current symptoms of AD/HD. Although patients with AD/HD showed poorer attention during continuous performance testing and more concurrent Axis I and II disorders (e.g., dysthymia, anxiety disorders including social phobia, APD) than those without AD/HD, the AD/HD diagnosis was not a significant predictor of decreased treatment retention, poor treatment compliance, or continuing substance abuse.

> [P]atients with severe symptoms may require longer, more intensive treatment.

Treatment Issues

General Treatment Considerations for Patients With Co-Occurring Disorders

Clearly, co-occurring disorders should not exclude people with opioid addiction from admission to an OTP. The consensus panel believes that the best strategy is to stabilize these patients' opioid addiction with methadone, buprenorphine, or levo-alpha acetyl methadol (LAAM) while assessing their co-occurring disorder symptoms and choosing the most appropriate treatment course. Although OTP staff members often focus on

the condition that is most severe and threatening, it usually is best to address all of a patient's disorders simultaneously because each can influence the others. TIP 42, *Substance Abuse Treatment for Persons With Co-Occurring Disorders* (CSAT 2005*b*), provides information about treatment planning and implementation for this group.

> [C]o-occurring disorders should not exclude people with opioid addiction from admission to an OTP.

The consensus panel believes that the following principles are essential to manage patients with co-occurring disorders in an OTP:

- Treatment of co-occurring disorders should be integrated or closely coordinated with substance abuse treatment when the former is not available on site.
- Staff members, whether primarily from the substance abuse treatment or mental health fields, should be knowledgeable about treatments for both disorders.
- Psychotropic medications should be prescribed only after patients are stabilized on the treatment medication (which in the panel's experience takes an average of 3 to 7 days for buprenorphine and 3 weeks to a month for methadone), unless an independent co-occurring disorder is evident from past records or clinical examination or significant impairment associated with the symptoms of a co-occurring disorder exists.
- All medications used by patients and patients' adherence to medication regimens should be monitored carefully, for example, via drug testing. Physicians should be careful about prescribing substances with abuse potential, such as benzodiazepines. If such medications are prescribed, the less abusable drugs in a class should be chosen, for example, oxazepam (Serax®) rather than lorazepam, clonazepam, alprazolam or diazepam.
- Patients resistant to being psychiatrically diagnosed should be assured that it is not shameful but is likely to provide a better understanding of their problems and aid in treatment. Educating patients about co-occurring disorders helps.
- Therapy for patients with co-occurring disorders should be more intensive, on average, than for patients without co-occurring disorders. The primary goal is abstinence from substances. Remission of co-occurring disorder symptoms should be an important secondary goal.

Co-Occurring Disorders and Treatment Planning

Because patients in MAT exhibit a wide range of co-occurring disorders, the consensus panel believes that early treatment planning and resource management should include classifying patients, at least tentatively, into categories based on types and severity of co-occurring disorders, although treatment always should be tailored individually.

Patients in acute psychiatric danger

Patients presenting with suicidal or homicidal ideation or threats—whether resulting from acute intoxication or withdrawal or from an independent co-occurring disorder—or those manifesting psychotic symptoms (e.g., hallucinations, paranoia) that may interfere with their safety and ability to function should be assessed and treated immediately. Although their symptoms may be short lived, admission to a psychiatric unit for brief treatment may be necessary if outpatient care is too risky or problematic. Immediate administration of antipsychotic drugs, benzodiazepines, or other sedatives may be required to establish behavioral control (Minkoff 2000). A physician, physician's assistant, or nurse practitioner on staff can prescribe medications at the OTP. Otherwise,

referral is warranted. In emergencies, OTPs should send patients to affiliated hospital emergency rooms (see "Handling Emergency Situations" below).

Patients with established, severe co-occurring disorders

Patients in MAT who are not in acute danger but have been diagnosed or treated for severe co-occurring disorders (e.g., schizophrenia, bipolar disorder) should receive medication with the lowest abuse potential for their condition. If an OTP is staffed appropriately and prepared to treat patients with severe co-occurring disorders, these patients can be treated on site. Otherwise, they should be referred to an OTP with these qualifications. If there is no such OTP, patients may need to remain in a less optimal OTP but receive psychiatric treatment at another facility. For referrals, effective communication between OTPs and mental health providers is necessary to coordinate treatment.

Patients with less severe, persisting or emerging symptoms of co-occurring disorders

Patients in MAT with nondisabling symptoms of less severe co-occurring disorders (e.g., mood, anxiety, and personality disorders), psychiatric treatment histories, or verified diagnoses and current prescriptions for medications to treat such disorders (regardless of whether they are used) should continue or begin medication, psychotherapy, or both for their co-occurring disorders. These patients should continue in MAT if the OTP is staffed to treat them. Although it is desirable for patients to be stabilized on methadone, buprenorphine, or LAAM before other pharmacotherapy is initiated, newer medications with relatively benign side effects can be initiated sooner (e.g., selective serotonin reuptake inhibitors [SSRIs]) if a primary mental disorder is indicated. Such medications may facilitate engagement in MAT and addiction recovery (Minkoff 2000).

Patients with less severe, presumptively substance-induced co-occurring disorders

The consensus panel recommends that patients in MAT with symptoms of Axis I disorders but no history of primary co-occurring disorders receive no new psychotropic medications until they are stabilized on MAT because their symptoms might remit or significantly diminish after a period of substance abuse treatment (Joe et al. 1995). Exceptions include patients who have acute, substance-induced disorders such as extreme anxiety or paranoia that are likely to be transitory but require temporary sedation or antianxiety medication.

Effects of Co-Occurring Disorders on HIV Risk Behaviors and Comorbidity

King and colleagues (2000) found that patients with co-occurring disorders in MAT were at higher risk for contracting and transmitting HIV than those without these disorders. In another study, patients who were HIV seropositive and had co-occurring disorders were more likely than those without co-occurring disorders to continue using drugs, less likely to be prescribed HIV medications or to adhere to medication regimens, and more likely to develop AIDS (Ferrando et al. 1996). People with co-occurring disorders, particularly depression or dysthymia, were more likely than those without Axis I disorders to continue needle sharing and other high-risk behaviors (Camacho et al. 1996). Patients in MAT who injected drugs and had APD were at higher risk for contracting and spreading HIV (Brooner et al. 1993). To decrease the spread of HIV, it is important to treat both substance use and co-occurring disorders and provide education and support for patients who inject drugs. More information on HIV/AIDS and substance abuse treatment, including the combined treatment of HIV/AIDS, substance abuse, and mental illness, can be found in TIP 37, *Substance Abuse Treatment for Persons With HIV/AIDS* (CSAT 2000*e*).

Models of Care

Although it is not always feasible to provide more specialized services on site, patient adherence to medical treatment was found to drop dramatically when such services were provided through offsite referral (Batki et al. 2002). Even when referrals are to services near an OTP, noncompliance may have significant consequences for personal, social, and public health.

If a program cannot provide onsite ancillary services, it is important that staff members identify co-occurring disorders early so that they can refer patients to appropriate resources. It is essential to monitor patient progress and compliance with offsite treatment, which can be done by a counselor, case manager, nurse, or physician's assistant or by assigning one staff member to coordinate and monitor all referrals. Offsite referrals also may be necessary to obtain psychotropic medications and evaluate patients' reactions to them.

Handling Emergency Situations

A high percentage of patients with co-occurring disorders in MAT have reported suicide attempts or difficulty controlling violent behavior during their lifetimes (Cacciola et al. 2001). Patients who present an acute danger to themselves or others or have psychotic symptoms or disordered thinking that could interfere with their safety or that of others should receive immediate, aggressive intervention on admission and throughout treatment. Staff members should be trained to notice indications of suicidal or homicidal risks. These observations should be documented and communicated to designated staff members who can take necessary action, including appropriate medication, notification of family members and involved agencies (e.g., probation office, children's protective services), or transfer of patients to more secure or protective settings. Staff members should understand thoroughly and be prepared to act on an OTP's "duty to warn" (CSAT 2004*b*) about potentially violent behavior by patients.

Risk factors and predictors for suicidal ideation and threats

People who are opioid addicted have high rates of suicide and attempted suicide, ranging from 8 to 17 percent in some studies with even higher rates among certain groups (Krausz et al. 1996). Substance intoxication or withdrawal can cause or exacerbate suicidal ideation or threats, and the presence of co-occurring disorders further increases the risk. Chapter 4 discusses risk factors for suicide and recommended treatment responses. Risk factors do not predict individual behavior, but a high-risk profile merits immediate and ongoing attention (Chatham et al. 1995*a*; Hall et al. 1999). In one study of suicidality among patients in an OTP, the strongest predictors of suicide risk were psychosocial dysfunction (e.g., depression, social withdrawal, hostility toward friends and family), help-seeking behaviors (e.g., previous treatment episodes, attendance at mutual-help meetings, self-referral), and perceived lack of support from others (Chatham et al. 1995*a*).

At least two studies of patients in MAT who overdosed on opioids concluded that overdoses usually were accidental and not predictive of subsequent suicide attempts. In an early work, Kosten and Rounsaville (1988) found that accidental overdoses were three times more likely than suicidal ones. More recently, Darke and Ross (2001) reported that 92 percent of patients who overdosed characterized the overdose as accidental. In that study, of the 40 percent who acknowledged a previous suicide attempt, only 10 percent deliberately overdosed with heroin compared, for example, with 21 percent who deliberately overdosed with benzodiazepines.

Protocol for identifying and handling suicide and homicide risk

All intake workers, certified addiction counselors, and clinicians should be alert to risk factors for suicide and homicide and should question at-risk patients routinely about suicidal or homicidal thoughts or plans. This is

important for patients who appear withdrawn, depressed, angry, or agitated or are known to have experienced a recent significant loss or other source of stress—especially if a co-occurring disorder is suspected or diagnosed or if a patient still is intoxicated or withdrawing from a psychoactive substance. Although the consensus panel believes such screening is helpful, the research evidence supporting its effectiveness is limited (Kachur and DiGuiseppi 1996).

To aid in screening and referral for suicidality and homicidality, all programs should have protocols in place that specify

- Who asks what questions or uses what specific tool to identify these types of risk
- How identified risks are documented
- Who is informed about risks and is responsible for taking actions and what resources he or she can use (e.g., medications, referral/transfer, family involvement).

Any patient suspected of suicide or homicide risk should be referred immediately to a mental health clinician for further evaluation. If the OTP has no psychologist, clinical social worker, or psychiatrist on staff, it should have arrangements for rapid consultations. Decisions should be made about using antipsychotic medications, benzodiazepines, or other sedatives to establish behavioral control rapidly (Minkoff 2000). Such medications may be needed to alleviate or control symptoms until other mood stabilizers or antidepressants take hold, which can take several weeks. Medication-assisted treatment of acute suicidality should be on an inpatient basis unless family members or friends are willing to be responsible for administering the drugs regularly, keeping the at-risk patient safe, and monitoring his or her reactions.

Patients identified as being at imminent risk of committing suicide or homicide might need hospitalization for short-term observation. Some key factors in this decision are clearly expressed intent, specific and lethal plans, accessible means, limited social or familial resources, severe symptoms of mental illness or psychosis, command hallucinations, hopelessness, and previous suicide or homicide attempts. If a referral is made, the patient should not be left alone until responsibility for monitoring safety is transferred to the referred facility.

Counseling, Psychotherapy, and Mutual-Help Groups for People With Co-Occurring Disorders in MAT

Chapter 8 discusses counseling, case management, and psychotherapy for patients in MAT. Programs should encourage participation in mutual-help groups that focus on the needs of people with co-occurring disorders. Exhibit 12-3 lists some of the best known of these groups, along with contact information.

Exhibit 12-3

Mutual-Help Groups for People With Co-Occurring Disorders

- Double Trouble in Recovery (www.doubletroubleinrecovery.org)
- Dual Recovery Anonymous (www.draonline.org)
- Dual Disorders Anonymous (847-781-1553 or P.O. Box 681268, Schaumburg, IL 60168)
- Dual Diagnosis Recovery Network (www.dualdiagnosis.org) (active mostly in California)

Psychoeducation for Patients With Co-Occurring Disorders in MAT

Group sessions presenting information about topical issues can help patients with co-occurring disorders and their families. Patients can explore relevant themes by emphasizing positive coping strategies and sharing experiences. Possible topics for psychoeductional groups are presented in Exhibit 12-4.

Pharmacotherapy for Patients With Co-Occurring Disorders in MAT

Several pharmacological treatments for co-occurring disorders are available and should be used when indicated. Most medications are more effective when used with counseling or psychotherapy in comprehensive MAT.

In many ways, an OTP is an optimal setting to initiate and monitor psychiatric pharmacotherapy for co-occurring disorders because patients attend daily (at least in the early stages of treatment) and onsite physicians and other staff can observe their reactions to psychotropic medications as well as to methadone or other addiction treatment medications.

When psychotropic medications are used in an OTP, they should be prescribed

- In a comprehensive program that integrates medical, psychiatric, and social interventions and supports patient compliance with medication dosing schedules.

Exhibit 12-4

Topics for Psychoeducational Groups for People With Co-Occurring Disorders

- Causes, symptoms, and treatment for substance use and co-occurring disorders
- Medical and mental effects of co-occurring disorders
- Psychosocial effects of co-occurring disorders
- The recovery process for co-occurring disorders
- Medications to treat co-occurring disorders, their side effects, and medication management
- Coping with cravings, anger, anxiety, boredom, and depression
- Changing negative or maladaptive thinking
- Developing a sober support system
- Addressing family issues
- Learning to use leisure time constructively
- Spirituality in recovery
- Joining 12-Step and co-occurring disorder recovery mutual-help groups
- Risk factors in ongoing recovery
- Understanding and getting maximum benefits from psychotherapy and counseling

Adapted from Daley 2000.

- In the context of a multidisciplinary-team approach in which regularly scheduled team meetings ensure that all members are aware of the patient's progress in treatment.
- With careful selection of medications because some patients may attempt to get high on any medication prescribed. Some medications (e.g., amitriptyline, tramadol, benzodiazepines) have little abuse potential in other populations but pose a significant risk of abuse in this population (Cicero et al. 1999).

If patients in an OTP are prescribed other medications in addition to addiction treatment medications, the consensus panel recommends the following procedures:

- All prescribed psychotropic medications should be to treat suspected or confirmed co-occurring disorders, not to alleviate normal discomfort (Minkoff 2000).
- Fixed, rather than "prn" or "as needed," doses of psychotropic medications should be prescribed because, especially early in MAT, patients addicted to opioids have difficulty regulating medications of any kind (Minkoff 2000). Whenever possible, given resource availability, potentially abusable medications should be dispensed by OTP staff along with addiction treatment medication.
- Patients receiving psychotropic medications should be educated about each drug's expected benefits, potential disadvantages and limitations, side effects, implications for pregnancy and breast-feeding, length of time before full effects should begin, and potential to cause tolerance and withdrawal. This education can be done individually or in a group, but all information should be communicated both in writing and orally.
- An onsite (full- or part-time) physician or psychiatrist should have regular contact with each patient with a co-occurring disorder to review medication response and compliance. This professional also should supervise counselor interactions with these patients and participate in team meetings to discuss treatment plans.

OTPs should consider a hierarchical approach to treating patients with co-occurring disorders, starting with psychosocial interventions such as increased counseling or psychotherapy (unless the patient has a disorder clearly needing medication). Depending on severity and acuity of symptoms, treatment providers may be able to use nonpharmacological approaches such as psychotherapy, either alone or with psychiatric medications. If these psychosocial approaches are ineffective or of limited benefit, providers should select psychiatric medications with the lowest abuse potential that are likely to be effective. TIP 37, *Substance Abuse Treatment for Persons With HIV/AIDS* (CSAT 2000*e*, pp. 83–84), provides a summary of abuse potential for psychiatric medications. The psychiatric medications should be, in most instances, adjunctive to other ongoing interventions, not a substitute for them. However, other factors to consider include

- The potential effect of medication side effects on compliance
- Potential negative interactions with addiction treatment medication or other drugs
- Lethality if the drug is used impulsively or intentionally for suicide
- Potential effects on a patient's physical condition—for example, whether the drug might injure an already damaged liver or increase blood pressure in a hypertensive patient.

Some studies have found that methadone may, by itself, relieve some symptoms of mood and anxiety disorders but not Axis II personality disorders (Calsyn et al. 2000*a*; Musselman and Kell 1995). From a practical viewpoint and assuming sufficient time to observe patients before further intervention, the consensus panel believes that the best approach is careful observation during the first weeks of MAT to determine whether symptoms of co-occurring disorders diminish before psychiatric medications are considered.

Medications for major depression and bipolar disorder

The hierarchical approach described in the previous two paragraphs for treating patients in MAT with co-occurring disorders should be used to determine which patients diagnosed with major depression or bipolar disorder may benefit from antidepressant medication. Exhibit 12-5 summarizes interactions of some

Exhibit 12-5

Interactions of Some Medications for Depression and Bipolar Disorder With Methadone and Recommended Treatment Response in MAT

Medication Type and Examples	Action With Methadone	Recommended Treatment Response
SSRIs fluvoxamine (Luvox®), fluoxetine (Prozac®), sertraline (Zoloft®)	Some SSRIs inhibit metabolism of methadone and increase methadone blood levels (Eap et al. 1997). Fluoxetine and sertraline do not increase methadone levels significantly. Fluvoxamine is the most dangerous SSRI and should be avoided for patients in MAT.	Observe patients carefully for signs of methadone overmedication during the first weeks of treatment with SSRIs. Methadone withdrawal symptoms may occur after discontinuation of fluvoxamine.
Carbamazepine (Tegretol®)	Carbamazepine speeds production of liver enzymes that metabolize methadone and can cause severe opioid withdrawal symptoms (Eap et al. 2002).	Avoid carbamazepine and use alternatives such as valproate (Depakote®). Increase and/or split the methadone dosage to increase its blood levels.
Tricyclics desipramine, nortriptyline, imipramine, doxepin	Methadone impairs the metabolism of tricyclics and can cause increased tricyclic medication blood levels (Maany et al. 1989).	Adjust doses of tricyclic medications as needed; monitor blood levels if clinically indicated.
Monoamine oxidase (MAO) inhibitors	MAO inhibitors may have dangerous interactions with certain foods and substances of abuse (Kleber 1983).	Use extreme caution in prescribing these medications in MAT.
Lithium	None.	Monitor closely because window between therapeutic and toxic dose is narrow.

antidepressant medications with methadone and recommended treatment response. Antidepressants have been used successfully to treat depression in patients in MAT. One example is a study of patients with chronic depression who were treated with the tricyclic imipramine or a placebo. Fifty-seven percent of imipramine-treated patients showed both significant improvement in mood and some decreases in illicit drug use according to self-reports, compared with only 7 percent of placebo patients who reported results (Nunes et al. 1998*a*). However, no significant reductions in substance use were found between the two groups based on drug testing. There is no theoretical reason to presume that tricyclic medications are unique among antidepressants improving mood, and SSRIs are much safer and may be the preferred treatment. Antidepressants also may be helpful for anxiety disorders.

Bipolar disorder in patients in MAT can be treated with antipsychotic or mood-stabilizing medications. Mood stabilizers shown to be effective include lithium, valproate, and carbamazepine (Hellewell 2002). Lamotrigine (Lamictal®) also has been shown to be effective.

Anxiety disorders

Anxiety disorders, including panic disorder, PTSD, and others, can be treated with psychotherapy, pharmacotherapy, or both. These disorders can be treated effectively with antidepressant medications such as the SSRIs, venlafaxine (Effexor®), and the tricyclics. Patients sometimes respond better to one drug class or a specific drug in a class. Therefore, another antidepressant should be considered if patients do not respond to their first one after a 4- to 8-week trial. Some antidepressants also have sedative effects (e.g., mirtazapine [Remeron®], trazodone, and some tricyclic antidepressants), which might be beneficial for patients with insomnia when these drugs are taken before bedtime, or for patients with high levels of anxiety. Nonsedating antidepressants might be especially useful for patients with psychomotor inhibition.

The well-documented abuse potential of benzodiazepines has led to a common belief that they are contraindicated in patients receiving methadone. However, evidence suggests major differences in the abuse liability of benzodiazepines. Those with a slower onset of action such as oxazepam rarely are mentioned as substances of abuse, have a wide margin of safety, and are effective in reducing anxiety, even over extended periods (Sellers et al. 1993). Several case reports have indicated that benzodiazepines, particularly those with low abuse liability, may be used safely for patients with substance use disorders (Adinoff 1992; Sellers et al. 1993). Sellers and colleagues also found a "serious pattern of nontherapeutic benzodiazepine use . . . among opiate-dependent persons, particularly those in methadone maintenance treatment programs" (1993, p. 72), leading these authors to recommend that "if benzodiazepine is used [with this group], those with an apparently low abuse potential are generally preferable."

The consensus panel believes that patients who have a history of benzodiazepine abuse should not be disallowed from receiving previously prescribed benzodiazepines, provided that they are monitored carefully and have stopped the earlier abuse. They may be attempting to reduce symptoms of co-occurring disorders, and, when they receive a prescribed medication with low abuse liability and are monitored for their co-occurring anxiety and substance use disorders, improvement and cessation of other benzodiazepine use may occur naturally. Some drug-testing laboratories can determine specific types of benzodiazepines used. If such a resource is available, testing can determine whether patients are using only their prescribed benzodiazepines or supplementing them with others obtained illicitly. The latter would indicate a need to change patients' treatment plans.

AD/HD

Stimulants such as methylphenidate (Ritalin®) are the treatment of choice for childhood AD/HD. Stimulant treatment in adulthood also is potentially effective but carries the obvious

risk of abuse by patients in MAT. Use of cocaine could be an attempt to control symptoms of AD/HD (Levin et al. 1998). If AD/HD is severe, treatment providers should consider treatment with medications such as methylphenidate, amphetamine, or atomoxetine (Strattera®) because these medications reduce AD/HD symptoms and address cocaine or other stimulant use. However, they should be monitored carefully because some patients have abused them by injection, and medical complications can result from long-term injection use. Tricyclic antidepressants also are effective for some patients in MAT with co-occurring AD/HD and depression (Higgins 1999), and these drugs carry no addiction liability. Recently, the nonstimulant atomoxetine was approved to treat AD/HD and may prove advantageous for patients in MAT with co-occurring AD/HD. However, because atomoxetine is metabolized by the cytochrome P450 system of liver enzymes, the potential for interaction with methadone exists, and it should be used cautiously until more information is available.

Schizophrenia

Patients in MAT who have schizophrenia often have profound impairment in thinking and behavior and are unlikely to fit in well in many OTPs. Antipsychotic medication, along with psychosocial intervention, is the mainstay of treatment. Newer atypical antipsychotic medications for schizophrenia are preferred over older "typical" agents, which carry a risk of movement disorders such as tardive dyskinesia, a neurological syndrome caused by long-term use of neuroleptic medications (National Institute of Neurological Disorders and Stroke 2001).

Newer antipsychotic medications (clozapine [Clozaril®, olanzapine [Zyprexa®], risperidone [Risperdal®]), quetiapine, ziprasidone [Geodon®], and aripiprazole [Abilify®]) have fewer side effects, are more effective in many cases, and should be considered as the initial treatment for some patients or as a second option for those not responding to more traditional medications. TIP 42, *Substance Abuse Treatment for Persons With Co-Occurring Disorders* (CSAT 2005*b*), provides more information.

Collaboration Between Counselors and Physicians

Many counselors have little or no psychiatric background and need training in

- Working with patients who may have co-occurring disorders but who resist evaluation or respond only partially to treatment
- Exploring stereotypes and feelings about what it means to have a co-occurring disorder
- Helping patients keep physician appointments, understand information, and follow physician recommendations
- Supporting patients to try medication if recommended
- Supporting patients to tolerate side effects long enough to determine whether medications help
- Providing guidance about when to contact a physician to report side effects or lack of relief from or worsening symptoms
- Supporting patients to continue taking medication, even when they feel better.

Physicians need training or guidance in

- Providing education to OTP staff about co-occurring disorders and medications
- Recognizing common misunderstandings about and resistances to medication in addiction treatment
- Creating protocols that make good use of counselor ability to provide detailed observations and ongoing feedback on patients' conditions (Zweben 2003).

Appendix 12-A. Internet Resources for Accessing Psychiatric Instruments

- **Comorbidity and Addictions Center: George Warren Brown School of Social Work** (www.gwbweb.wustl.edu/Users/cac/measurescollection.htm). Lists 175 instruments for measuring aspects of substance use and psychopathology with hyperlinks to descriptions. Information for each measure or scale includes purpose, authors, key references, target populations, variables, administration and scoring options, and time estimates as well as copyright, cost, and ordering information.
- **Medical Outcomes Systems, Inc.** (www.medical-outcomes.com). Contains a description of the Mini International Neuropsychiatric Interview as well as downloadable versions of all M.I.N.I. instruments, including the screen version and standard and expanded (Plus) 5.0.0 editions (January 2002). Although materials are protected by copyright, researchers and clinicians working in nonprofit or publicly owned settings (e.g., universities, teaching hospitals, government institutions) may make copies for clinical or research purposes.
- **National Institute on Alcohol Abuse and Alcoholism** (www.niaaa.nih.gov/publications). Provides access to information first published in *Assessing Alcohol Problems: A Guide for Clinicians and Researchers* (Allen and Columbus 1995). The site specifies useful measures for screening, diagnosing, and planning treatment for alcohol-related and other psychoactive substance use disorders, as well as co-occurring disorders. The site also includes information on administration and scoring options, estimated times for administration, key variables, groups on which normative data for the instrument were based, psychometric properties, and ordering costs.
- **University of Adelaide (Australia) Library Guide** (www.library.adelaide.edu.au/guide/med/menthealth/scales.html). Contains a list of psychiatric rating scales and information about where copies and descriptions of these instruments can be obtained, hyperlinks to electronic versions, and references on developmental history and psychometric properties of each instrument.

13 Medication-Assisted Treatment for Opioid Addiction During Pregnancy

In This Chapter...

Little information exists on the prevalence of opioid use by pregnant women, but there is some information about opioid use by pregnant women entering substance abuse treatment programs. Of the 400,000 women admitted to programs in 1999, 4 percent were pregnant when admitted. Opioids were the primary substance of abuse for 19 percent of both pregnant and nonpregnant women who entered these programs (Office of Applied Studies 2002).

Acceptance of Methadone Maintenance as the Standard of Care

Methadone has been accepted since the late 1970s to treat opioid addiction during pregnancy (Kaltenbach et al. 1998; Kandall et al. 1999). In 1998, a National Institutes of Health consensus panel recommended methadone maintenance as the standard of care for pregnant women with opioid addiction (National Institutes of Health Consensus Development Panel 1998). Methadone currently is the only opioid medication approved by the U.S. Food and Drug Administration (FDA) for medication-assisted treatment for opioid addiction (MAT) in pregnant patients. Buprenorphine is classified as a category C drug by FDA (i.e., one lacking adequate, well-controlled studies in pregnant women) and, at this writing, is not FDA approved to treat pregnant women, although several studies have found it safe and effective in this group (e.g., Fischer et al. 2000; Lacroix et al. 2004). Even though it is a category C drug, buprenorphine may be used with pregnant patients in the United States under certain circumstances (see "Use of Buprenorphine During Pregnancy" later in this chapter).

Effective medical maintenance treatment with methadone has the same benefits for pregnant patients as for patients in general. In addition, methadone substantially reduces fluctuations in maternal serum opioid levels, so it protects a fetus from repeated withdrawal episodes

(Kaltenbach et al. 1998). Comprehensive methadone maintenance treatment that includes prenatal care reduces the risk of obstetrical and fetal complications, in utero growth retardation, and neonatal morbidity and mortality (Finnegan 1991).

Diagnosing Opioid Addiction in Pregnant Patients

In the consensus panel's experience, some women who are opioid addicted do not acknowledge pregnancy readily, or they misinterpret early signs of pregnancy, for example, fatigue, headaches, nausea and vomiting, and cramps, as opioid withdrawal symptoms. Consequently, onset of pregnancy may cause these patients to increase their use of illicit opioids or other substances that do not alleviate their perceived withdrawal symptoms but expose their fetuses to increased serum levels of these substances.

Many women who are opioid addicted confuse the amenorrhea caused by their stressful, unhealthful lifestyles with infertility. They might have been sexually active for years without using contraceptives and becoming pregnant. The consensus panel has noted that, because methadone normalizes endocrine functions, it is not unusual for women in the early phases of MAT to become pregnant unintentionally, especially if they receive no counseling for this possibility.

Procedures for diagnosing opioid and other addictions in pregnant women should incorporate information from their medical and substance use histories, physical examinations, drug test reports, and observed signs or symptoms of withdrawal. Other indications of addiction may include evidence of diseases associated with drug use (e.g., hepatitis, bacterial endocarditis, cellulitis), poor attendance for prenatal care, and unexplained fetal growth abnormalities (e.g., intrauterine growth retardation). Using an opioid antagonist to diagnose addiction in pregnant women is *absolutely contraindicated* (Finnegan 1991); inducing even mild withdrawal can cause premature labor or other adverse fetal effects.

Medical and Obstetrical Concerns and Complications

Pregnant women who abuse substances, including alcohol and nicotine, have a greater-than-normal risk of medical complications. These women should be monitored regularly for signs of anemia, poor nutrition, increased blood pressure, hyperglycemia, sexually transmitted diseases (STDs), hepatitis, preeclampsia, and other complications of pregnancy or health problems related to addiction. Good nutrition, including vitamin supplements, should be encouraged. Pregnant women should be educated about the potential adverse effects of substance use on their fetuses, such as fetal alcohol syndrome and premature labor associated with opioid withdrawal or stimulant use. Patient use of prescribed medications other than methadone should be monitored for compliance with usage directions and for adverse effects.

Chronic substance use in pregnancy can cause medical complications (some are listed in Exhibit 13-1), depending on how substances are administered and when or whether problems are identified and treated. Infections account for a high percentage of these complications in pregnant women who are opioid addicted, as they do in all people who abuse opioids (see chapter 10). Infections can be profoundly harmful to both women and their fetuses, particularly if infections remain unrecognized and untreated during gestation. Hepatitis B and C, bacterial endocarditis, septicemia, tetanus, cellulitis, and STDs are especially frequent (Finnegan 1991).

The rate of vertical perinatal transmission of hepatitis B virus (HBV) is high (ranging from 70 to more than 90 percent [Centers for Disease Control 1988*b*; Ranger-Rogez et al. 2002]), especially if a pregnant woman has active infection (determined by a positive

Exhibit 13-1

Common Medical Complications Among Pregnant Women Who Are Opioid Addicted

Anemia	STDs
Bacteremia/septicemia	Chlamydia
Cardiac disease, especially endocarditis	Condyloma acuminatum
Cellulitis	Gonorrhea
Depression and other mental disorders	Herpes
Edema	HIV/AIDS
Gestational diabetes	Syphilis
Hepatitis (acute and chronic)	Tetanus
Hypertension/tachycardia	Tuberculosis
Phlebitis	Urinary tract infections
Pneumonia	Cystitis
Poor dental hygiene	Pyelonephritis
	Urethritis

Adapted from Finnegan 1979.

hepatitis B antigen test) in the third trimester or within 5 weeks postpartum. If a new mother's hepatitis B antigen test is positive, the neonate should receive both hepatitis B vaccine and hepatitis B immune globulin (Kaltenbach et al. 1998). The rate of perinatal transmission of hepatitis C virus (HCV) is lower than that of HBV, as discussed below; however, vaccines exist for hepatitis A virus and HBV but not for HCV. Recommended laboratory tests for pregnant women who are opioid addicted are listed in Exhibit 13-2.

HCV

Pregnant women with a history of injection drug use are at high risk for HCV infection and should be screened for anti-HCV antibody. HCV ribonucleic acid (RNA) testing should be performed if an anti-HCV antibody test is positive. The results facilitate referral for further evaluation, staging, and treatment of liver disease after delivery. Infants whose mothers have hepatitis C should receive HCV RNA testing along with antibody testing for HCV between ages 2 and 6 months and again between 18 and 24 months (Roberts and Yeung 2002).

During pregnancy, HCV can be transmitted vertically from mother to fetus. However, multiple studies have shown low overall HCV vertical transmission risk and greater risk from factors such as HIV co-infection or high HCV viral load (Roberts and Yeung 2002). Vaginal delivery and breast-feeding do not appear to increase the risk of neonatal HCV infection significantly (Dinsmoor 2001; Roberts and Yeung 2002). Available treatments to prevent vertical

Exhibit 13-2

Laboratory Tests for Pregnant Women Who Are Opioid Addicted

• Complete blood count with differential and platelets • Chemistry screen (K, Na, Cl, Ca, P, CO_2, creatinine, blood glucose, blood urea nitrogen, total bilirubin, total serum protein albumin) • Hepatic panel (liver function tests) • Hepatitis B surface antigen (full panel if positive) • Hepatitis C antibody • Rubella titer • Serology (Venereal Disease Research Laboratory or Rapid Plasma Reagin tests) • Sickle prep (if appropriate) • Blood type; Rh and indirect Coombs Varicella (if unsure of history) • HIV (with counseling)	• Urine tests Urinalysis—routine and microscopic Urine culture and sensitivity Urine drug screen • Tuberculin skin test (Mantoux) • Alpha-fetoprotein between 15 and 21 weeks' gestation (optimal, 16 to 18 weeks) • 1-hour, 50 mg glucose challenge test at 24 to 28 weeks' gestation (at initial visit if risk factors) • Repeat complete blood count and serology at 24 to 28 weeks' gestation • Group B Strep vaginal-rectal culture at 35 to 37 weeks' gestation

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transmission, however, are limited by the fetal toxicity of the medications currently available for HCV infection.

HIV/AIDS

Pregnant women who are opioid addicted and HIV positive present a unique treatment problem. A limited number of studies with small numbers of patients have examined the relationship of HIV, methadone, and immune function (e.g., Beck et al. 2002; Siddiqui et al. 1993). These studies have not been replicated widely. Therefore, it is difficult to conclude any significant relationship involving HIV, methadone, and immune function until additional studies are completed. Studies on the combined effects of HIV antiretroviral treatment and methadone especially are needed.

During the early 1990s, before effective prevention treatments were available, studies in North America and Europe found mother-to-child or perinatal HIV transmission rates of 16 to 25 percent. However, between 1996 and 2000, after the implementation of new guidelines, studies in the United States found transmission rates of 5 to 6 percent, and more recent studies have found rates below 2 percent when antenatal antiretroviral drugs or zidovudine (AZT) is combined with cesarean section (Centers for

Disease Control and Prevention 2001*b*). Although AZT prophylaxis reduces the risk of perinatal HIV infection, monotherapy often is inadequate to treat a mother's HIV disease. Combination antiretroviral therapy is now the standard of care (Paul et al. 2001).

Studies in the United States and Europe have found that pregnancy has no effect on HIV progression (Burns et al. 1998; Saada et al. 2000). Studies before the availability of antiretroviral therapy showed no increase in prematurity, low birth weight, or intrauterine growth restriction associated with HIV infection. These data are difficult to interpret because of relatively high rates of adverse events in the control groups attributed to other conditions such as substance abuse (Brocklehurst and French 1998; Bucceri et al. 1997). Studies have not found increases in birth defects or fetal malformation related to HIV infection (Brocklehurst and French 1998).

The consensus panel recommends that women who are opioid addicted and HIV infected receive additional counseling and support during the postpartum period to improve their adherence to antiretroviral therapy and to meet the demands of caring for a newborn. Breast-feeding by HIV-infected women has been associated with an increased risk of HIV transmission and should be discouraged (Nduati et al. 2000).

Obstetrical Complications

Obstetrical complications in pregnant women who are opioid addicted are the same as those seen at increased rates in all women who lack prenatal care (see Exhibit 13-3). These complications may be difficult to diagnose in patients who are opioid addicted because they often deny the existence of complications or avoid medical settings. When obstetrical complications are confirmed, standard treatments, including use of medications to arrest preterm labor, can be initiated safely.

Methadone Dosage and Management

The pharmacology of methadone in pregnant women has been evaluated thoroughly. Methadone is distributed widely throughout

Exhibit 13-3

Common Obstetrical Complications Among Women Addicted to Opioids

Abruptio placentae	Postpartum hemorrhage
Chorioamnionitis	Preeclampsia
Intrauterine death	Premature labor/delivery
Intrauterine growth retardation	Premature rupture of membranes
Intrauterine passage of meconium	Septic thrombophlebitis
Low Apgar scores	Spontaneous abortion
Placental insufficiency	

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the body after oral ingestion, with extensive nonspecific tissue binding creating reservoirs that release unchanged methadone back into the blood, contributing to methadone's long duration of action (Dole and Kreek 1973). Peak plasma levels occur between 2 and 6 hours after a maintenance dose of methadone is ingested, with less than 6 percent of the ingested dose in the total blood volume at this time. Lower sustained plasma concentrations are present during the remainder of a 24-hour period (Stine et al. 2003).

As pregnancy progresses, the same methadone dosage produces lower blood methadone levels, owing to increased fluid volume, a larger tissue reservoir for methadone, and altered opioid metabolism in both the placenta and fetus (Weaver 2003). Women who are methadone maintained often experience symptoms of withdrawal in later stages of pregnancy and require dosage increases to maintain blood levels of methadone and avoid withdrawal symptoms (Jarvis et al. 1999; Kaltenbach et al. 1998). The daily dose can be increased and administered singly or split into twice-daily doses (Kaltenbach et al. 1998).

> [M]ethadone dosages for pregnant women [should] be determined individually to achieve an effective therapeutic level.

Historically, treatment providers have based dosing decisions on the need to avoid or reduce the incidence of neonatal abstinence syndrome (NAS) (Kaltenbach et al. 1998; Kandall et al. 1999) rather than to achieve an effective therapeutic dosage. This low-dose approach, which emerged from several 1970s studies (e.g., Harper et al. 1977; Madden et al. 1977), has been contradicted by more recent studies (e.g., Brown et al. 1998; Kaltenbach and Comfort 1997). The consensus panel knows of no compelling evidence supporting reduced maternal methadone dosages to avoid NAS. On the contrary, higher dosages have been associated with increased weight gain, decreased illegal drug use, and improved compliance with prenatal care by pregnant women in MAT and with increased birth weight and head circumference, prolonged gestation, and improved growth of infants born to women in MAT (De Petrillo and Rice 1995; Hagopian et al. 1996). Moreover, reduced methadone dosages may result in continued substance use and increase risks to both expectant mothers and their fetuses (Archie 1998; Kaltenbach et al. 1998). The consensus panel recommends that methadone dosages for pregnant women be determined individually to achieve an effective therapeutic level.

Induction and Stabilization

Methadone dosages for pregnant women should be based on the same criteria as those for women who are not pregnant. Women who received methadone before pregnancy should be maintained initially at their prepregnancy dosage. However, if pregnant women have not been maintained on methadone, the consensus panel recommends that they either be inducted in an outpatient setting by standard procedures or be admitted to a hospital (for an average stay of 3 days) to evaluate their prenatal health status, document physiologic dependence, and initiate methadone maintenance if possible.

For pregnant women being inducted in an outpatient setting, a widely accepted protocol is to give initial methadone doses of 10 to 20 mg per day, with exact dosage based on a patient's opioid use history. A patient should be asked to return at the end of the day for followup evaluation, and the initial dose may be followed by regular adjustments of 5 to 10 mg based on therapeutic response (Archie 1998). Twice daily observation should continue until the patient is stabilized. If evidence of intoxication or withdrawal emerges, treatment providers should adjust the patient's dosage immediately. Most pregnant women can be stabilized within

48 to 72 hours (Kaltenbach et al. 1998). In outpatient settings, where fetal monitors usually are unavailable, it is crucial that patients record measures of fetal movement at set intervals (Jarvis and Schnoll 1995).

Split Dosing

Split-dosing methadone regimens are accepted widely for pregnant patients, but little empirical investigation has been done of its effects on fetuses or maternal plasma levels (Jarvis et al. 1999). Although split dosing may improve maternal compliance with treatment and decrease cocaine use (De Petrillo and Rice 1995), traveling to an opioid treatment program (OTP) twice a day or, for unstable or newly admitted patients, qualifying for take-home medication doses may be difficult.

Managing Polysubstance Use

A large percentage of pregnant women in MAT—up to 88 percent in one study—continue to use other substances including alcohol, nicotine, heroin, cocaine, barbiturates, and tranquilizers (Edelin et al. 1988). The risks of other substance use for both maternal and fetal health are well documented (Reid 1996). It is essential that patients be monitored for use of both licit and illicit drugs and alcohol to manage appropriately the perinatal care of both mothers and infants (Kaltenbach et al. 1998).

Polysubstance use is a special concern during pregnancy because of the adverse effects of cross-tolerance, drug interactions, and potentiation (Kaltenbach et al. 1998) and the serious maternal and fetal health risks from continued substance use and lack of adequate prenatal care (Svikis et al. 1997*a*). Chapter 11 provides more information about treatment of multiple substance abuse in MAT; the forthcoming TIP *Substance Abuse Treatment: Addressing the Specific Needs of Women* (CSAT forthcoming *f*) contains additional information on the effects of different substances on pregnant women.

Management of Acute Opioid Overdose in Pregnancy

Opioid overdose in pregnancy threatens both pregnant women and their fetuses. Naloxone, a short-acting, pure opioid antagonist, is the pharmacological treatment of choice for opioid overdose but should be given to pregnant patients only as a last resort (Weaver 2003). Patients should receive naloxone (0.01 mg/kg of body weight) intravenously after an airway is established to ensure adequate respiration. Patients can receive additional naloxone doses every 5 minutes after they regain consciousness. Naloxone's duration of action is from 30 minutes to 2 hours, depending on the dose and type of substance that was used, whereas that of most opioids is from 6 to 8 hours and that of methadone or other long-acting opioids (e.g., morphine sulfate contin, OxyContin®) is from 12 to 48 hours (or more for levo-alpha acetyl methadol). Therefore, symptoms are likely to recur within 30 minutes to 2 hours of naloxone treatment, and treatment providers should continue administering naloxone intravenously or intramuscularly at intervals until the effects of illicit opioids markedly diminish, which may take 2 to 3 days. Special care is needed to avoid acute opioid withdrawal that can harm a fetus. Treatment providers should titrate the naloxone dose against withdrawal symptoms and use a short-acting opioid to reverse acute withdrawal symptoms (Archie 1998).

Managing Withdrawal From Methadone

Withdrawal from methadone, called medically supervised withdrawal (MSW) or dose tapering, is not recommended for pregnant women. When MSW is considered, however, a thorough assessment is important to determine whether a woman is an appropriate candidate for MSW because the procedure frequently results in relapse to opioid use. Appropriate patients for MSW during pregnancy include those who

- Live where methadone maintenance is unavailable
- Have been stable in MAT and request MSW before delivery
- Refuse to be maintained on methadone
- Plan to undergo MSW through a structured treatment program (Archie 1998; Kaltenbach et al. 1998).

A patient who elects to withdraw from methadone should do so only under supervision by a physician experienced in perinatal addiction treatment, and the patient should receive fetal monitoring. MSW usually is conducted in the second trimester because the danger of miscarriage may increase in the first trimester and the danger of premature delivery or fetal death may increase in the third trimester (Kaltenbach et al. 1998; Ward et al. 1998*a*). However, the consensus panel has found no systematic studies on whether withdrawal should be initiated only during the second trimester. If MSW is undertaken, methadone should be decreased by 1.0 to 2.5 mg per day for inpatients and by 2.5 to 10.0 mg per week for outpatients. Fetal movement should be monitored twice daily in outpatients, and stress tests should be performed at least twice a week; MSW should be discontinued if it causes fetal stress or threatens to cause preterm labor (Archie 1998; Kaltenbach et al. 1998).

Postpartum Treatment of Mothers in MAT

Current treatment practices include continuing methadone after delivery either at dosages similar to those before pregnancy or, for women who began methadone maintenance during pregnancy, at approximately half the dosages they received in the third trimester. However, no empirical data support these approaches, and any decrease should be based on signs of overmedication, withdrawal symptoms, or patient blood plasma levels (Kaltenbach et al. 1998).

Breast-Feeding

Mothers maintained on methadone can breast-feed if they are not HIV positive, are not abusing substances, and do not have a disease or infection in which breast-feeding is contraindicated (Kaltenbach et al. 1993). Hepatitis C is no longer considered a contraindication for breast-feeding.

The American Academy of Pediatrics has a longstanding recommendation (1983) that methadone is compatible with breast-feeding only if mothers receive no more than 20 mg in 24 hours. However, studies have found minimal transmission of methadone in breast milk regardless of maternal dose (Geraghty et al. 1997; Wojnar-Horton et al. 1997). McCarthy and Posey (2000) found only small amounts of methadone in breast milk of women maintained on daily doses up to 180 mg and argued that available scientific evidence does not support dosage limits of 20 mg a day for nursing women.

Effects on Neonatal Outcome

NAS

Infants prenatally exposed to opioids have a high incidence of NAS, characterized by hyperactivity of the central and autonomic nervous systems that is reflected in changes in the gastrointestinal tract and respiratory system. Infants with NAS often suck frantically on their fists or thumbs but may have extreme difficulty feeding because their sucking reflex is uncoordinated (Kaltenbach et al. 1998). Withdrawal symptoms may begin from minutes or hours after birth to 2 weeks later, but most appear within 72 hours. Preterm infants usually have milder symptoms and delayed onset. Many factors influence NAS onset, including the types of substances used by mothers, timing and dosage of methadone before delivery, characteristics of labor, type and amount of anesthesia or analgesic during labor, infant maturity and

nutrition, metabolic rate of the infant's liver, and presence of intrinsic disease in infants. NAS may be mild and transient, delayed in onset or incremental in severity, or biphasic in its course, including acute neonatal withdrawal signs followed by improvement and then onset of subacute withdrawal (Kaltenbach et al. 1998). Although NAS can be more severe or prolonged with methadone than heroin because of methadone's longer half-life, with appropriate pharmacotherapy, NAS can be treated satisfactorily without any severe neonatal effects.

Onset of NAS may be delayed by other neonatal illnesses. In addition, various other conditions may mimic NAS, such as hypoglycemia, hypocalcemia, sepsis, and neurological illnesses. To rule out such conditions, infants suspected of having NAS should have a complete blood cell count with differential, electrolyte and calcium levels, comprehensive neurological consultation, and head ultrasound if indicated.

An abstinence scoring system should be used to monitor opioid-exposed newborns to assess the onset, progression, and diminution of symptoms (Kaltenbach et al. 1998). The Neonatal Abstinence Score (Finnegan and Kaltenbach 1992) is used widely to estimate NAS severity, determine whether pharmacotherapy is needed, and monitor the optimum response to therapy. All infants of mothers with an opioid use history should be scored every 4 hours. Control is achieved when the average Neonatal Abstinence Score is less than 8, infants exhibit rhythmic feeding and sleep cycles, and infants have optimal weight gains.

If pharmacological management is indicated, several methods have been found useful. The American Academy of Pediatrics Committee on Drugs policy statement on Neonatal Drug Withdrawal (1998) describes several agents for the treatment of NAS including methadone, tincture of opium, paregoric, and morphine. One method (J. Greenspan, Thomas Jefferson University Hospital, Philadelphia, personal communication, October 2006) uses neonatal opium solution (0.4 mg/mL morphine-equivalent; starting dosage, 0.4 mg/kg/day orally in six to eight divided doses [timed with the feeding schedule]). Dosage is increased by 0.04 mg/kg/dose until control is achieved or a maximum of 2.0 mg/kg/day is reached. If Neonatal Abstinence Scores stay high but daily dosage nears maximum, symptoms are reassessed and concurrent phenobarbital therapy considered. When control is achieved, the dosage is continued for 72 hours before pharmacological weaning, in which dosages are decreased 10 percent daily or as tolerated. When 0.2 mg/kg/day is reached, medication may be stopped. Decisions about dosage decrease during pharmacological weaning are based on Neonatal Abstinence Scores, weight, and physical exams.

Maternal Methadone Dosage and Extent of NAS

The relationship between maternal methadone dosage and NAS has been difficult to establish, and the consensus panel believes no compelling evidence shows that methadone reduction avoids NAS. Although a number of investigators have reported significant relationships between neonatal withdrawal and maternal methadone dosage (e.g., Malpas et al. 1995; Mayes and Carroll 1996), most have found no such relationship (e.g., Berghella et al. 2003; Brown et al. 1998).

Perinatal Outcomes

Another area of concern is the intrauterine growth of infants born to women maintained on methadone. Early research yielded somewhat inconsistent findings, and not much new has been added since the 1980s. Studies comparing infants born to women addicted to heroin but not receiving methadone with infants born to women receiving methadone found differential effects, with reduced fetal mortality and greater birth weights indicated for

…NAS can be treated satisfactorily without any severe neonatal effects.

infants of women maintained on methadone (Connaughton et al. 1977; Kandall et al. 1977). Some studies comparing infants born to women not using opioids with infants of women in methadone treatment found lower birth weights in the latter group (Chasnoff et al. 1982; Lifschitz et al. 1983), whereas others found no differences in birth weights (Rosen and Johnson 1982; Strauss et al. 1976).

A study by Kaltenbach and Finnegan (1987) with 268 infants found that those exposed to methadone had lower birth weights and smaller head circumferences than those not exposed to drugs. However, the infants exposed to methadone were not small for their gestational age, and there was a positive correlation between head circumference and birth weight in both groups. These data suggested that infants born to women who are opioid addicted and maintained on methadone may have lower birth weights and smaller head circumferences than non–drug-exposed comparison infants, but the former are not growth restricted.

Researchers (e.g., Chasnoff et al. 1984; Jeremy and Hans 1985) who used the Brazelton Neonatal Behavioral Assessment Scale (Brazelton 1984) to investigate neurobehavioral characteristics in newborns undergoing opioid withdrawal have found differences consistently in behavior between these infants and infants born to women not opioid addicted. Infants exposed to opioids were more irritable, exhibited more tremors, and had increased muscle tone. Several studies have reported less responsiveness to visual stimuli and reduced alertness among infants exposed to opioids (Strauss et al. 1975).

> [I]nfants born to women who are opioid addicted and maintained on methadone may have lower birth weights and smaller head circumferences…

Important aspects of these behavioral characteristics are their implications for mother–infant interactions. In the consensus panel's experience, these infants are frequently difficult to nurture, causing poor mother–infant bonding, which Hoegerman and colleagues (1990) suggested might be the most devastating legacy of perinatal addiction.

Developmental Sequelae

Research on developmental sequelae associated with in utero methadone exposure has found that infants through 2-year-olds function well within the normal developmental range (e.g., Kaltenbach and Finnegan 1986; Rosen and Johnson 1982). Lifschitz and associates (1985) found no significant developmental differences between children of mothers maintained on methadone and children of mothers still using heroin or using no opioids, when sociodemographic, biological, and other health factors were considered. Other data have suggested that maternal drug use is not the most important factor in how opioid-exposed infants and children develop but that family characteristics and functioning play a significant role (Johnson et al. 1987). More information is needed to update or extend these findings from the 1970s and 1980s.

Use of Buprenorphine During Pregnancy

Buprenorphine use for pregnant women has not been approved in the United States, although it may be used with pregnant patients under certain circumstances (see below). It may be a safe and effective treatment for some pregnant women who are opioid addicted, but more research is needed. Several animal studies have been conducted. However, only limited prospective and open-label studies using sublingual buprenorphine tablets in pregnant women have been reported, and these represent the most closely controlled data (e.g.,

Johnson et al. 2001; Lejeune et al. 2002). Several case studies have been reported, mainly in France, of buprenorphine use during pregnancy (e.g., Marquet et al. 1997, 1998). Johnson and colleagues (2003*a*) provided a complete review of these reports. The studies all found that buprenorphine was well accepted by mothers and infants during the early neonatal stage and appeared useful to treat pregnant women who were opioid addicted.

In view of incomplete data and the absence of FDA approval for use of buprenorphine in pregnant patients, the consensus panel recommends that buprenorphine be used only when the prescribing physician believes that the potential benefits justify the risks. For example, patients already maintained and stable on buprenorphine who become pregnant probably should continue on buprenorphine with careful monitoring. Pregnant women who are opioid addicted but cannot tolerate methadone, those for whom program compliance has been difficult, or those who are adamant about avoiding methadone may be good candidates for buprenorphine. In such circumstances, it should be clearly documented in the patient's medical record that she has refused methadone maintenance treatment or that such services are unavailable; that she was informed of the risks of using buprenorphine, a medication that has not been thoroughly studied in pregnancy; and that she understands these risks. When treating pregnant patients, treatment providers should use buprenorphine monotherapy tablets (Subutex®) because no work has been done on the effects of fetal exposure to sublingual naloxone in buprenorphine-naloxone combination tablets (Suboxone®) during pregnancy. Consensus panelists have found that a patient already maintained on buprenorphine-naloxone combination tablets who becomes pregnant can be transferred directly to buprenorphine monotherapy tablets.

A more detailed discussion on buprenorphine use in the treatment and management of pregnant patients and its effects in newborns can be found in TIP 40, *Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction* (CSAT 2004*a*). For a comprehensive review of buprenorphine use in pregnant patients and its effects on the neonate, see the article by Johnson and colleagues (2003*a*). Current data indicate that buprenorphine probably is safe and effective for some women who are pregnant and opioid addicted, but more research is needed.

Buprenorphine Effects on NAS

Johnson and colleagues (2003*a*) reviewed 21 reports of buprenorphine use during pregnancy, most from Europe, and found that NAS was reported in 62 percent of approximately 309 infants exposed to buprenorphine, with 48 percent requiring treatment and 40 percent confounded by other drug use. Another study of 100 infants of mothers maintained on buprenorphine found NAS in approximately 67 percent (Johnson et al. 2001). Of these, 53 percent required treatment for withdrawal, and approximately 7 percent were admitted to a neonatal intensive care unit. Similar to infants born to women receiving methadone, infants of women receiving comprehensive prenatal care plus buprenorphine had improved birth outcomes compared with those whose mothers received no comprehensive prenatal care.

Buprenorphine-associated NAS generally appears within 12 to 48 hours, peaks at 72 to 96 hours, and lasts 120 to 168 hours, although some reports have indicated buprenorphine-related NAS lasting 6 to 10 weeks. Buprenorphine-associated NAS was found to be less intense than that associated with methadone (Johnson et al. 2003*a*). If controlled randomized trials confirm that newborns of mothers treated with buprenorphine have less NAS than those of mothers treated with methadone, it may be appropriate to switch patients from methadone to buprenorphine during early pregnancy to reduce chances for marked withdrawal syndromes in newborns.

Breast-Feeding During Buprenorphine Treatment

Research has indicated that only small amounts of buprenorphine and buprenorphine-naloxone pass into breast milk, with little or no effect on infants (Johnson et al. 2001; Schindler et al. 2003; CSAT 2004*a*). These data are inconsistent with product labeling, which advises against breast-feeding in mothers treated with buprenorphine or the buprenorphine-naloxone combination. Based on research data, particularly findings that buprenorphine is likely to be poorly absorbed by infants via the oral route, the consensus panel recommends that women maintained on buprenorphine be encouraged to breast-feed because of the benefits to infants and mother–child interaction. The panel recommends more research, particularly to confirm that infants absorb little buprenorphine during breast-feeding.

Importance of Integrated, Comprehensive Services

Pregnant women who are opioid addicted need comprehensive treatment services, including individual, group, and family therapy to address both the physiological and psychological effects of substance use and psychosocial factors. Psychosocial complications may include disruption of the mother–child relationship, guilt over the adverse effects of addiction on the family, and family adjustment when a newborn is retained in the hospital. Problems associated with domestic violence, financial support, food, housing, and childcare issues can be overwhelming to women in recovery and should be addressed. AIDS prevention, counseling, testing, and educational services should be available during prenatal and parenting classes. Services should be aimed at eliminating substance use, developing personal resources, improving family and interpersonal relationships, eliminating socially destructive behavior, and helping new parents cope with their environment.

Integrated services, whether on site or through linkages to other community-based agencies, encourage prospective patients to enter a treatment program and continue treatment. Services should be woman centered and directly address traumatic events. The array of services may include

- Special groups to address problems of pregnant women who are opioid addicted
- Available treatments for women addicted to opioids, including pharmacotherapies
- Education and discussion groups on parenting and childcare
- Special groups and services for children and other family members
- Couples counseling
- Case management and assistance in locating safe, affordable housing.

The forthcoming TIP *Substance Abuse Treatment: Addressing the Specific Needs of Women* (CSAT forthcoming *f*) has more detailed information on the psychosocial components of women-centered treatment.

Psychosocial Barriers

Women addicted to opioids typically face financial, social, and psychological difficulties that affect their options and treatment progress. Many have histories of negative experiences with the legal system or children's protective services that may cause them to be resistant to or noncompliant with treatment. Guilt and shame coupled with low self-esteem and self-efficacy can produce behaviors difficult for some staff members to tolerate, such as lateness, missed appointments, continued illegal drug use, and demanding or provocative behaviors. For successful treatment, care should be provided in a gender-specific, nonpunitive, nonjudgmental, nurturing manner, with attention to each patient's fears and cultural beliefs (Kaltenbach et al. 1998; Ward et al. 1998*a*).

Contingency Management Treatment Strategies

As discussed in chapter 8, contingency management strategies offering positive reinforcement for behavioral change have been effective in treating a range of substance use disorders. Voucher-based reinforcement therapy (VBRT) has been particularly effective in increasing abstinence from substances and strengthening behaviors such as compliance with treatment plans and participation in vocational training (Kidorf et al. 1998; Petry 2000; Silverman et al. 1996). These and other studies also have suggested that VBRT may help manage polysubstance abuse and improve retention for pregnant women in MAT.

Although few systematic studies have been done with pregnant women who are opioid addicted, available evidence has indicated that positive-contingency rewards for abstinence or treatment attendance can improve pregnancy outcomes (Chang et al. 1992; Jones et al. 2001). Contingency management incentives for this population have ranged from cash (Carroll et al. 1995; Chang et al. 1992) to vouchers exchangeable for goods and services (Jones et al. 2000, 2001; Svikis et al. 1997*b*).

Carroll and colleagues (1995) compared the effectiveness of an enhanced treatment program for pregnant patients that included a contingency management component, in which clients could earn $15 weekly for three consecutive negative drug tests, with an unenhanced treatment program. The group receiving enhanced treatment had better neonatal outcomes, but the two groups did not differ in percentages of positive drug tests. The authors attributed these results primarily to more frequent prenatal care in the contingency management group. However, results of the study were limited by the small sample size (seven women in each group), the inability to discern which components contributed to improved outcomes, and use of a demanding contingency procedure that reinforced continuous abstinence (e.g., three consecutive negative drug tests) but not discrete abstinence (each negative drug test).

Many pregnant women who receive MAT discontinue treatment prematurely, with the highest dropout rates occurring on transfer from residential to outpatient treatment. A related series of controlled, randomized studies (Jones et al. 2000, 2001; Svikis et al. 1997*b*) examined whether brief voucher incentives improved patient participation and decreased substance use during this transition phase. In pregnant women maintained on methadone, low-value incentives did not influence substance use (Jones et al. 2000). However, greater incentives, using an escalating reinforcement procedure, both decreased substance use and increased full-day outpatient treatment attendance (Jones et al. 2001).

Overall, these studies have suggested that contingency management using positive rewards for desired behaviors may be an important adjunct to MAT for pregnant women. It is noteworthy that interventions such as VBRT not only are compatible with MAT but address both continued substance abuse and poor program attendance.

> Integrated services… encourage prospective patients to enter a treatment program and continue treatment.

Nutrition Assessment, Counseling, and Assistance

People with substance use disorders often are poorly nourished. Substances themselves may impair users' metabolism, interfere with nutrient availability, and affect appetite. However, other lifestyle factors associated with substance use play a significant role, including poverty, poor eating and exercise habits, lack of concern

about nutrition and health, and diets restricted by physiological conditions.

Pregnancy is an opportune time to help women improve their health-related attitudes and behaviors. The consensus panel recommends that all pregnant patients in MAT receive

- An assessment of nutritional status, eating habits, and weight
- Education on appropriate diet and weight to meet optimal targets for the pregnancy
- Counseling to ensure that special nutrition-related medical and psychosocial problems are addressed—with high priority given to stopping or substantially reducing cigarette, alcohol, and other substance use with known adverse effects on fetuses
- Supplemental nutrients when nutritional needs cannot be met by diet changes
- Information about and referral to food assistance programs.

Nutritional Education for Pregnant Patients in MAT

Most pregnant women in MAT can benefit from nutritional guidance that encourages them to have wholesome, well-balanced diets consistent with their ethnic or cultural backgrounds and financial situations. Such guidance helps them understand how diet and substance use affect the fetus, pregnancy, labor and delivery, and breast-feeding.

Some OTPs have trained nurses or other staff members who facilitate a nutrition education program. In addition, the National Center for Nutrition and Dietetics of the American Dietetic Association (800-366-1655 or www.eatright.org) refers inquirers to registered dietitians in the local area who provide individual or group counseling or program information about diet during pregnancy. Another useful resource, *Pregnancy and Nutrition*, a seven-page pamphlet developed by the National Women's Health Information Center (www.4women.gov/faq/preg-nutr.htm), covers recommended dietary allowances for pregnant women, diet changes and weight gain, cravings, exercise, dietary supplements, diabetes, morning sickness, and nausea.

OTPs wishing to assess patients' knowledge about nutrition might be interested in the U.S. Department of Agriculture's 22-page survey forms (www.barc.usda.gov/bhnrc/foodsurvey) to ascertain respondents' knowledge of nutrition, food composition, labeling requirements, and serving sizes, as well as eating habits and attitudes.

Food Program Assistance for Pregnant Patients in MAT

Pregnant women in MAT who are nutritionally at risk or financially needy may be eligible for supplemental food assistance. Their school-age children also might qualify for school breakfast and lunch programs, as well as summer food programs. OTP counselors should be familiar with the services and requirements of each type of program and make appropriate referrals. Facts about food stamps can be found at www.fns.usda.gov/fns. Information about the Federal Women, Infants, and Children program can be accessed at www.fns.usda.gov/wic or www.nal.usda.gov/wicworks.