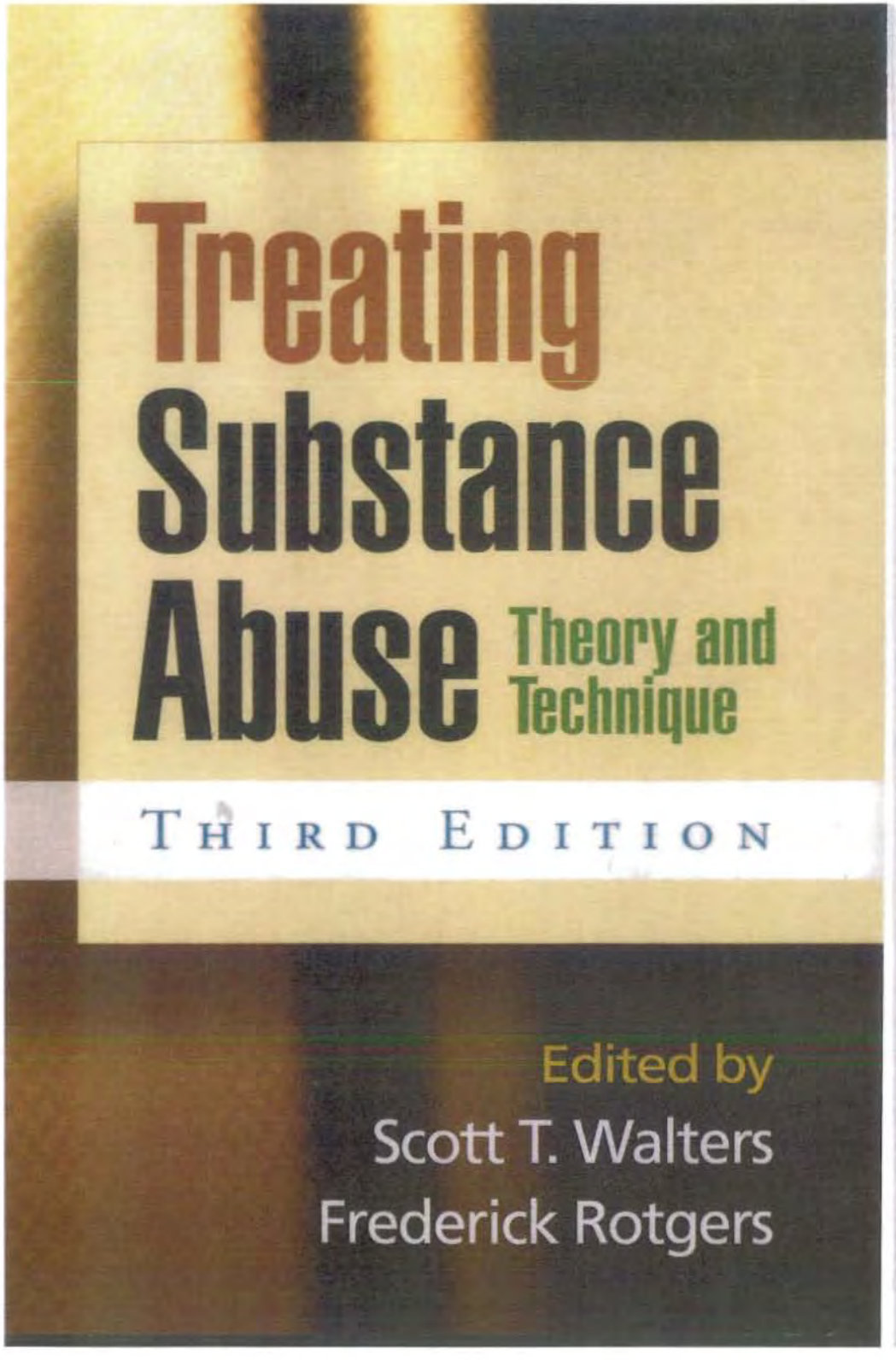

Treating Substance Abuse

Theory and Technique

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Chapter 11

Neurobiological Bases of Addiction Treatment

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Over the past two decades stunning progress has been made in understanding the psychopathology of addiction. These advances have identified changes in neural pathways that evolve following chronic substance use. Substance-induced alterations in brain functioning have both physiological (tolerance and dependence) and behavioral consequences, such as craving and the inability to control the impulse to use drugs despite adverse consequences—the defining characteristic of addiction. Neuroimaging technologies have been used to study the brain and the reinforcing and addictive properties of substances. In a parallel effort, genetic risk factors have been identified that predispose individuals to addictive disorders. Understanding that addiction has a fundamental biological component helps explain the difficulty that many people have in achieving and maintaining abstinence without pharmacological treatment. On the basis of this medical model of addiction, several medications have been developed to assist in normalizing the brain chemistry disrupted by chronic substance use or aid in the avoidance of substance use. By providing this support, new medications allow addicted individuals to focus on their psychosocial treatment and work a program of recovery.

This chapter first presents the basics of brain function, including the neurotransmitters and pathways involved in substance abuse. This understanding provides the foundation for the subsequent presentation of medications used to treat addictive disorders. This chapter focuses on medications approved by the U.S. Food and Drug Administration (FDA) for alcohol dependence and opioid dependence with an overview of promising new developments for stimulant and cannabis dependence. (Carroll & Kiluk, Chapter 12, this volume) in this book talks more specifically about integrating psychotherapy with pharmacotherapy.

Brain Basics

Neurons and the Brain

Microscopically, the brain is composed of a collection of cells, or *neurons*, that signal one another both chemically and electrically. Electrical signals are used to communicate within cells, and chemical signals are used to communicate between cells. Most neurons have a characteristic structure that consists of a globular *cell body* with numerous long, spindly projections coming off the central cell body (Figure 11.1). These projections are used in the process of signaling between neurons and receive communications from their sometimes-distant cell bodies. The *axon* of a signaling cell projects to the *dendrite* of the receiving cell, and the two projections come into close proximity with one another but do not touch. This coming together of the axon of the signaling cell and the dendrite of the receiving cell is the *synapse*, and the space between the two projections is the *synaptic cleft* (Figure 11.2). Cells are either *presynaptic* or *postsynaptic* to indicate the location

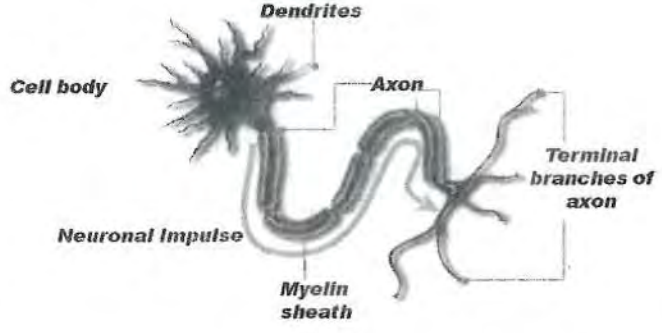

FIGURE 11.1. Structure of a neuron. Both axons and dendrites project from the central cell body. Electrical impulses travel down the axon, which is insulated by the myelin sheath, to the terminal branches of the axon. Adapted from the National Institutes of Health Image Bank.

of the cell relative to the signaling process being studied. The presynaptic cell is the cell that is sending the message; the postsynaptic cell is the cell that is receiving the message. When a neuron fires electrically, or *depolarizes*, a message is carried from one part of a cell to its projections. Neuronal firing causes the release of chemical *neurotransmitters* (e.g., dopamine) into the synapse that carry signals across the synaptic cleft from one neuron to another (Figure 11.2). At rest, neurotransmitters are stored in *vesicles* at the terminal ends of the axon of the presynaptic cell. When the cells depolarize, the vesicles fuse with the cell membrane, and a neurotransmitter is released from the presynaptic cell into the synaptic cleft. The neurotransmitter then diffuses out across the small space of the synaptic cleft to contact the postsynaptic cell membrane. *Receptors* on the postsynaptic cell membrane are proteins that await the arrival of specific neurotransmitters, much like a lock awaiting a specific key. The binding of the neurotransmitter to the receptor then activates that receptor, which in turn transmits a signal into the postsynaptic cell. Many receptors and neurotransmitter systems have been implicated in the neurobiology of substance abuse, including dopamine, serotonin, norepinephrine, glutamate, gamma-aminobutyric acid (GABA), acetylcholine, the endogenous opiate system, and the cannabinoid system (Kandel, Schwartz, & Jessell, 2000).

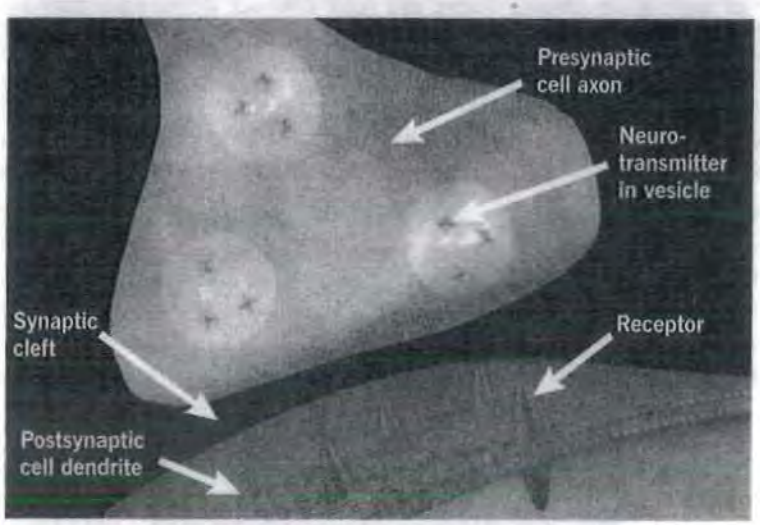

FIGURE 11.2. Structure of a synapse. Cells signal one another via synapses. In response to an electrical impulse, neurotransmitters are released from vesicles in the presynaptic cell axon. The neurotransmitters diffuse across the synaptic cleft to bind to receptors on the postsynaptic cell membrane. Adapted from the National Institutes of Health Image Bank.

Neuroanatomy Basics

On a larger scale, the brain is composed of the brainstem, the basal ganglia, and the cortex (Figure 11.3), as well as the many thousands of connections, or *tracts*, between these structures (Nolte, 2009). The brainstem is the most interior and primitive area of the brain. Several anatomical areas in the brainstem are thought to be involved in the pathogenesis of addictive behaviors, including the *ventral tegmental area (VTA), substantia nigra (SN)*, and *dorsal raphe nucleus (DRN)*. The area between the brainstem and the cortex is the basal ganglia and is made up of distinct areas, many of which are involved in the development and persistence of addiction. These include the *nucleus accumbens (NAc), bed nucleus of the stria terminalis (BNST)*, and *amygdala*. The outermost and most evolutionarily advanced anatomical area of the brain is the cortex, which communicates to the rest of the brain via the *thalamus*. Several cortical areas are implicated in the pathogenesis of drug-taking behaviors, including the *anterior cingulate cortex, dorsolateral prefrontal cortex, orbitofrontal cortex, insular cortex*, and *hippocampus* (Figure 11.4).

Neuroanatomy of Substance Abuse

The neurotransmitter dopamine is particularly important in the neurobiology of substance abuse. There are four distinct dopamine pathways in the brain: the mesolimbic pathway, the mesocortical pathway, the nigrostriatal pathway, and the tuberoinfundibular pathway (Figure 11.4). The first dopamine pathway in the brain is the *mesolimbic pathway*, which is composed of cells in the ventral tegmental area that project to the nucleus accumbens. It was originally thought that the release of dopamine in the

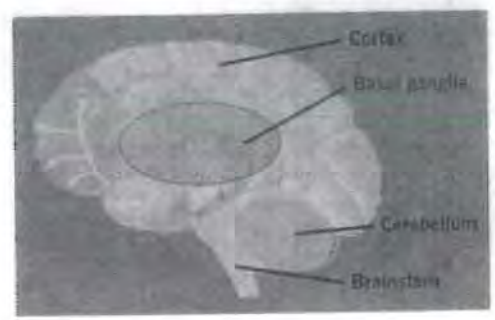

FIGURE 11.3. Major anatomical divisions of the brain. The brainstem is at the base of the brain. The basal ganglia are located on top of the brainstem. The cortex is the outermost structure, and the cerebellum sits off the back of the brain. Adapted from the National Institutes of Health Image Bank.

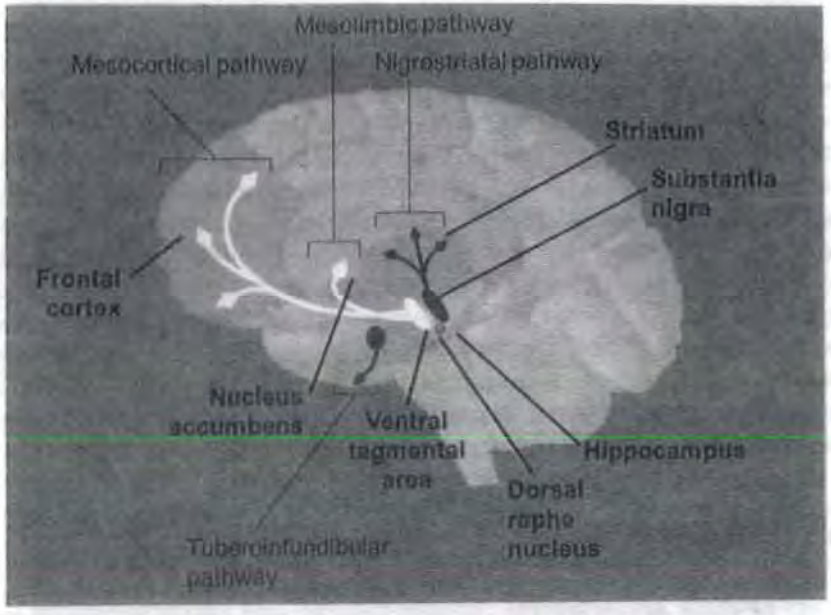

FIGURE 11.4. Brain areas involved in the neurobiology of addiction. Labeled in bold are the frontal cortex, nucleus accumbens, ventral tegmental area, dorsal raphe nucleus, hippocampus, substantia nigra, and striatum. Also represented are the four dopamine pathways in the brain: the mesolimbic pathway (white), the mesocortical pathway (white), the nigrostriatal pathway (gray), and the tuberoinfundibular pathway (gray). Adapted from the National Institutes of Health Image Bank.

nucleus accumbens was the neurobiological substrate that accounted for the experience of pleasure. However, further study suggested that the brain mechanisms underlying substance abuse were more complicated than first hypothesized. Dopamine cells of the mesolimbic pathway also project to a variety of other subcortical structures, including the amygdala, bed nucleus of the stria terminalis (BNST), lateral septal area, and lateral hypothalamus, which are also involved in the pathogenesis of substance abuse.

The second dopamine pathway in the brain is the *mesocortical pathway*, which consists of cells in the ventral tegmental area whose projections extend to cerebral cortical structures, especially the frontal lobes. This pathway is important for cognitive function, motivation, and emotional responses. It includes several cerebral cortical structures believed to have an important role in the addictive process, such as the dorsolateral prefrontal cortex (Dagher, Owen, Boecker, & Brooks, 1999), the orbitofrontal cortex (Elliott, Dolan, & Frith, 2000; Kringelbach, 2005), and the anterior cingulate (Allman, Hakeem, Erwin, Nimchinsky, & Hof, 2001; Bush, Luu,

& Posner, 2000). This neural system may contribute to the development of addiction in several ways. The prefrontal cortex is important in allowing people to control impulsive behavior. Hence, disruptions or abnormalities in this area of the brain may lead to increased impulsivity and subsequent drug use. In addition, the impaired ability of this circuit to inhibit behaviors may be involved in craving, the progression of drug use from impulsive to compulsive use and relapse. The third dopamine pathway in the brain is the *nigrostriatal pathway*, which consists of a collection of dopamine cells in the substantia nigra (adjacent to the ventral tegmental area) that project to the striatum. This pathway is involved in the production of movement in the normal brain (Nicola, Surmeier, & Malenka, 2000) and can account for the motor effects of some drugs of abuse (Gardner & Ashby, 2000). The fourth dopamine pathway is the *tuberoinfundibular pathway* and does not play a significant role in substance abuse.

Reward and Drug Taking

Drugs of abuse act on several different receptor and neurotransmitter systems (Gardner, 1997). However, the activation of dopamine-rich cells in the ventral tegmental area and the subsequent release of dopamine in the nucleus accumbens is particularly important because it is associated with reward. This biochemical phenomenon is observed with both natural pleasurable stimuli (e.g., food and sex) and a variety of drugs of abuse (e.g., alcohol, amphetamine, caffeine, cocaine, marijuana, nicotine, opiods, and phencyclidine) (Adinoff, 2004).

Drugs are classified by the response caused in a cell after they bind to their respective receptors. An *agonist* is a drug that stimulates (turns on) a response in a cell after binding to a receptor. An *antagonist* is a drug that blocks (turns off) the response caused by the agonist. A *partial agonist* is a drug that binds to and activates a receptor to a lesser degree when compared to a full agonist. Stimulant drugs such as cocaine (Ritz, Lamb, Goldberg, & Kuhar, 1987) and amphetamine (Bunney & Aghajanian, 1978) work to directly increase the concentration of dopamine in the nucleus accumbens by binding to proteins on the presynaptic membrane of the dopamine cell itself, but many other drugs of abuse work indirectly to increase dopamine in the nucleus accumbens. Some substances of abuse bind to receptors and cause downstream changes inside the cell that indirectly increase dopamine in the nucleus accumbens. For instance, tetrahydrocannabinol (THC, the active ingredient in marijuana) binds to and activates cannabinoid receptors throughout the brain. Opiods (i.e., heroin and morphine) bind to and activate opiod receptors in the ventral tegmental area, nucleus accumbens, and amygdala. Caffeine binds to and inactivates adenosine A2

receptors in the striatum. Alcohol and benzodiazepines increase activity of the GABA receptor. Alcohol also decreases functioning of the *N*-methyl-D-aspartate (NMDA) glutamate receptor. Phencyclidine (PCP) binds to the NMDA receptor and blocks ion movement through the channel in the protein. Nicotine binds to and activates nicotinic acetylcholine receptors. Each brain receptor that binds with an abused substance has a corresponding endogenous compound that is the natural key to unlock the activity of that receptor. For example, the endogenous endorphins and enkephalins bind to the opioid receptors, acetylcholine binds to the nicotinic receptor, and anandamide binds to the cannabinoid receptors. Many of the receptor and neurotransmitter systems serve as targets for existing and developing pharmacological treatment strategies for substance abusers.

However, dopamine increases alone do not fully explain the highly complex phenomenon of substance abuse, which has biological, developmental, social, learned, and psychological components. What makes a drug addictive is not directly proportionate to its primary site of action. There are two models that attempt to explain this complex relationship. In the *opponent processes* model, a drug of abuse produces euphoria (positive affective state) when acutely administered and dysphoria (negative affective state) when access to the drug is prevented. The withdrawal dysphoria is associated with decreased dopamine levels in the nucleus accumbens (Jentsch, Olausson, De La Garza, & Taylor, 2002) and may augment the transition from substance use to compulsive substance abuse (Koob & Le Moal, 2005). Substance-abusing individuals also exhibit drug-seeking behaviors at the expense of natural rewards. In the *incentive salience* model, addictive behavior is thought to form by associative learning that enhances the incentive salience (or importance) of drug-related cues in relation to natural rewards. This leaves the individual with a long-term vulnerability to relapse (Kalivas & Volkow, 2005). With continued drug use, there is a shift in how the brain imparts relative importance to different stimuli, from long-term reinforcers (e.g., healthy relationships, successful occupations) to short-term reinforcers associated with substance use. There is also thought to be behavioral sensitization, with repeated exposures to a drug of abuse, in which the impulsive liking of a drug for pure hedonic value is replaced by a more compulsive wanting of the drug with concomitant loss of control over inhibitory behaviors (Robinson & Berridge, 2000). In this way, the teaching of Alcoholics Anonymous (AA) to avoid people, places, and things associated with use is supported by neurobiological research, as these conditioned cues cause an activation of certain brain structures that lead a substance user to crave drugs of abuse.

The process of addiction itself has been conceptualized in three stages: binge, withdrawal, and craving. Each stage has been mapped onto particular anatomical areas in the brain (Koob & Volkow, 2010). In the *binge*

stage, the ventral tegmental area and the nucleus accumbens (or ventral striatum) mediates the acute reinforcing effects of drugs of abuse. The transition from impulsive use to compulsive abuse is associated with a shift in activity from the ventral striatum to the dorsal striatum and orbitofrontal cortex. *Withdrawal* from drugs of abuse results from a period of acute abstinence after a prolonged period of consistent use and is associated with observable brain changes. It is associated with decreased dopamine activation in the nucleus accumbens and is mediated by the amygdala. *Craving* describes an intense desire to use a substance and can be triggered by use of a small amount of the drug itself (Self & Nestler, 1998) or by cues that are associated with drug use (Jentsch et al., 2002). The effects of craving are thought to be mediated by a wider network consisting of the orbitofrontal cortex, dorsal striatum, prefrontal cortex, amygdala, hippocampus, and insula. The consolidation of memories that leads to craving is likely mediated by the neurotransmitter glutamate and involves the amygdala and hippocampus as well as cortical regions such as the orbitofrontal cortex and the anterior cingulate cortex. Also associated with substance abuse and relapse is a decreased ability to inhibit certain behaviors (e.g., drug use), which is mediated by the cingulate cortex, the dorsolateral prefrontal cortex, and the inferior frontal cortices. Because of the loss of these higher brain functions, there is an emergence of behaviors associated with shorter term, immediate reward (Goldstein & Volkow, 2002). The inability to inhibit behaviors, often a risk factor for the development of substance abuse, also becomes increasingly impaired. Thus, there appears to be a lack of willpower in the ability to further resist substance use and relapse (Adinoff et al., 2007). The changes that occur in the brain as a result of substance abuse are complex; many do not return to predrug use levels even after prolonged abstinence. While some of the detailed neurobiological changes are still to be elucidated, it is clear there are dramatic shifts in brain functioning that result from substance abuse. Table 11.1 summarizes the areas of the brain that are involved in addictive behavior.

Medications for Substance Abuse

This section discusses the current pharmacological treatment options for the major classes of abused drugs. (The integrations of pharmacology and psychotherapy are discussed in Chapter 12.) These include medications approved by the FDA for alcohol and opioid addiction, as well as promising medications for the treatment of cocaine, methamphetamine, and cannabis addiction. Medications are presented in sections organized by specific drugs of abuse. For each medication, background information as well as clinically relevant considerations are included that should be of benefit to substance abuse treatment providers.

TABLE 11.1. Brain Areas Involved in Addiction

Amygdala	• Subcortical structure • Consolidation of emotional memories (Paton, Belova, Morrison, & Salzman, 2006) • Fear conditioning (LeDoux, 2003)
Anterior cingulate cortex	• Cortical structure • Modulation of emotional responses, impulsivity (Bush et al., 2000) • Error detection, problem solving (Allman et al., 2001)
Bed nucleus of the stria terminalis (BNST)	• Subcortical structure • Major output pathway of the amygdala (Choi et al., 2007) • Reactions to fearful stimuli (Fox et al., 2010) and stress (Somerville, Whalen, & Kelley, 2010)
Dorsal raphe nucleus (DRN)	• Midbrain structure • Location of serotonin cell bodies that project widely throughout the brain (O'Hearn & Molliver, 1984) • Regulates arousal and vigilance (Abrams et al., 2005) • Modulates activity of the ventral tegmental area (Yoshimoto & McBride, 1992)
Dorsolateral prefrontal cortex (DLPFC)	• Cortical structure • Planning, sequencing, and cognitive control (Dagher et al., 1999)
Hippocampus	• Primitive cortex • Long-term memory (Canales, 2010) and spatial navigation (Sharma, Rakoczy, & Brown-Borg, 2010)
Insular cortex	• Cortical structure • Processing negative emotional experience (Critchley, Wiens, Rotshtein, Ohman, & Dolan, 2004) and pain (Baliki, Geha, & Apkarian, 2009) • Integrating information from multiple sensory modalities (Taylor, Seminowicz, & Davis, 2009)
Nucleus accumbens (NAc)	• Subcortical structure, part of the ventral striatum • Regulation of reward (Willuhn, Wanat, Clark, & Phillips, 2010) • Response to fear (Schwienbacher, Fendt, Richardson, & Schnitzler, 2004) • Response to novelty (Legault & Wise, 2001)
Orbitofrontal cortex (OFC)	• Cortical structure • Decision making (Kringelbach, 2005) and impulsivity in novel situations (Elliott et al., 2000)
Striatum	• Subcortical structure, composed of caudate and putamen • Regulation of motor activity (Voorn, Vanderschuren, Groenewegen, Robbins, & Pennartz, 2004)

(cont.)

TABLE 11.1. *(cont.)*

Substantia nigra (SN)	• Midbrain structure • Location of dopamine cell bodies that are the origin of the nigrostriatal dopamine circuit • Regulation of movement (Nicola et al., 2000)
Thalamus	• Between cerebral cortex and midbrain • Relay area for information into and out of the cerebral cortex (Jones, 2007)
Ventral tegmental area (VTA)	• Midbrain structure • Location of dopamine cell bodies that are the origin of the mesolimbic and mesocortical dopamine circuits • Drug and natural reward circuitry (Alcaro, Huber, & Panksepp, 2007)

Alcohol Dependence

Naltrexone

Naltrexone is an opioid receptor antagonist that is approved by the FDA for treatment of alcohol dependence in an oral formulation and an intramuscular, sustained-release formulation. It is also approved for the treatment of opioid dependence (see "Opioids").

History. Naltrexone was originally developed as a treatment for heroin dependence in the 1960s. In 1994, after several studies demonstrated its efficacy in treating alcohol-dependent individuals (O'Malley et al., 1992; Volpicelli, Alterman, Hayashida, & O'Brien, 1992), naltrexone was approved by the FDA for the treatment of alcohol dependence. In 2006, the FDA approved the sustained-release formulation, which is given by monthly intramuscular injection. This format may benefit patients with difficulties adhering to medication.

Pharmacology. Naltrexone appears to disrupt the rewarding and reinforcing effects of alcohol through its effects on the opioid receptor and, subsequently, dopamine release. In animal models, naltrexone administration decreases dopamine release, thereby attenuating reinforcement from alcohol (Benjamin, Grant, & Pohorecky, 1993). Naltrexone may also interfere with the transmission of reward signals by blocking stimulation of the opioid receptors by endogenous opioid compounds (endorphins, enkephalins, and dynorphins) (Morris, Hopwood, Whelan, Gardiner, & Drummond, 2001). Consistent with the postulated mechanism of decreasing the reward associated with alcohol, naltrexone decreases heavy drinking more than it increases abstinence (Pettinati et al., 2006).

Evidence and Research. The COMBINE (Combined Pharmacotherapies and Behavioral Interventions Study) trial evaluated the comparative efficacy of naltrexone, acamprosate, and behavioral interventions for treatment of opioid addiction. Naltrexone was found to be highly effective in decreasing drinking in treated subjects (Anton et al., 2006). A meta-analysis (a study that combines the results of multiple smaller studies to increase the statistical strength) of 24 naltrexone trials found that naltrexone decreased the risk of relapse in short-term treatment (up to 12 weeks), relative to placebo. Longer treatment courses (12 weeks or longer) resulted primarily in improvements in time to first drink and craving (Srisurapanont & Jarusuraisin, 2005). A review of 29 studies similarly found that most studies demonstrated decreased heavy or excessive drinking outcomes, rather than improved abstinence rates, with naltrexone versus placebo (Pettinati et al., 2006). A study of the sustained-release formulation of naltrexone (Vivitrol) demonstrated both its safety and efficacy in reducing the number of heavy drinking days (Kranzler, Modesto-Lowe, & Nuwayser, 1998).

Formulation and Dosing. Naltrexone hydrochloride (ReVia and Depade) is available in 50-mg tablets and is taken orally. Dosing typically begins with 25 mg (half-tablet) daily for up to 1 week with a subsequent increase to a maintenance dose of 50 mg daily. Most studies have tested the efficacy of the 50-mg dose, so there is limited data assessing the efficacy of the higher dose (100 mg) that is frequently prescribed. The sustained-release formulation (Vivitrol) comes in a 380-mg solution that is administered by intramuscular injection once every 4 weeks by a trained clinician.

Side Effects. The most common side effects are nausea, headache, dizziness, nervousness, fatigue, insomnia, vomiting, anxiety, and somnolence.

Contraindications and Safety. The main concerns when prescribing naltrexone are inducing opioid withdrawal in patients who have been using opioids and hepatotoxicity (see "Opioid Dependence").

Pregnancy. All medications approved by the FDA are assigned a Pregnancy Category classification based on evidence of risk to the fetuses of pregnant women. Data come from animal and/or human studies. All FDA-approved medications in this chapter are classified as Pregnancy Category C. This indicates that animal studies have demonstrated adverse effects on the fetus, but there are no adequate human studies to assess the risk in human fetuses. For this category, the potential benefits may justify use in pregnant women following a thorough informed consent discussion.

Acamprosate

Acamprosate is a relatively new medication that is FDA-approved for the treatment of alcohol dependence, specifically for maintenance of abstinence from alcohol use.

History. Acamprosate was originally developed in Europe and has been in use there since the 1980s for alcohol dependence treatment. It was approved in the United States by the FDA in 2004.

Pharmacology. Acamprosate helps normalize glutamate neurotransmitter systems altered by chronic alcohol consumption (Mason & Heyser, 2010). Acamprosate, a structural analogue of the inhibitory neurotransmitter GABA, may attenuate alcohol withdrawal symptoms by depressing the neuronal hyperexcitable state associated with withdrawal. The primary mechanism appears to be suppression of the excitatory glutamate neurotransmitter system (Wilde & Wagstaff, 1997). Normalization of glutamate neurotransmission may account for its reported ability to decrease cravings and subsequent alcohol intake. Craving can be conceptualized as the anticipation of the delivery of a positive reinforcing effect (e.g., pleasant intoxication symptoms) or conversely, the removal of a negative reinforcing effect (e.g., unpleasant withdrawal symptoms). By diminishing withdrawal symptoms through inhibition of the excitatory glutamate system acamprosate may reduce craving and thereby increase abstinence from alcohol (Littleton, 1995).

Evidence and Research. A meta-analysis of 33 trials demonstrated that acamprosate was safe and well tolerated, increased abstinence and compliance with treatment, and decreased relapses to alcohol (Bouza, Angeles, Munoz, & Amate, 2004). The COMBINE study (described in the naltrexone section), however, found acamprosate to be no more effective than placebo (Anton et al., 2006).

Formulation and Dosing. Acamprosate (Campral) is available in 333-mg oral tablets. Typical dosing is 666 mg three times daily for an approximate daily total of 2 grams. It should not be used for patients who are actively drinking as it is approved for the maintenance of abstinence from alcohol and not for decreasing alcohol intake. It can be safely given to patients with liver disease because it is eliminated from the body mostly by the kidneys.

Side Effects. Acamprosate tends to be well tolerated without serious side effects. The most common side effects include diarrhea, nausea, flatulence, and headaches.

Contraindications and Safety. Acamprosate should be lowered to 333 mg three times daily in patients with mild to moderate renal impairment and should not be given to those with severe impairment. Studies have also shown a significant but small increase in suicidal and depressive symptoms versus placebo (1.4% vs. 0.5% in studies lasting 6 months or less, and 2.4% vs. 0.8% in yearlong studies).

Pregnancy. Acamprosate is classified as a Pregnancy Class C medication by the FDA (see "Alcohol Dependence").

Disulfiram

Disulfiram is the oldest FDA-approved medication for treatment of alcohol dependence.

History. Disulfiram has been used since the 19th century in the production of rubber. An American physician working at a chemical plant in 1949 discovered its potential use in treating alcoholism. He had observed workers exposed to disulfiram becoming sober due to adverse physical reactions they had after subsequently drinking alcohol. Ten years later, scientists in Denmark studying disulfiram as a treatment for parasitic infections observed the same phenomenon in staff exposed to disulfiram who subsequently consumed alcohol (Suh, Pettinati, Kampman, & O'Brien, 2006). This led to investigations into its potential for the treatment of alcohol dependence and its eventual approval by the FDA over 50 years ago.

Pharmacology. The body normally metabolizes alcohol in a three-step process. Alcohol is first converted (using the enzyme alcohol dehydrogenase) to the toxic intermediate compound acetaldehyde. Acetaldehyde dehydrogenase then converts acetaldehyde into acetic acid, which is further converted to water and carbon dioxide. Disulfiram blocks the action of acetaldehyde dehydrogenase, preventing the conversion of acetaldehyde into acetic acid. This means that a person taking disulfiram who then consumes alcohol will experience a buildup of toxic acetaldehyde, which manifests as unpleasant physiological symptoms, including facial flushing, headache, diaphoresis, tachycardia, nausea, vomiting, palpitation, and hyperventilation (Petersen, 1992). These symptoms typically emerge within 20 minutes of alcohol intake and can last for up to several hours. More dangerous symptoms include convulsions, cardiovascular collapse, respiratory depression, arrhythmias, and myocardial infarction (Suh et al., 2006).

Patients taking disulfiram must avoid even small amounts of alcohol, as consumption of even small quantities can lead to severe symptoms. Conceptually, disulfiram therapy works as a form of operant learning with the

unpleasant physiological reaction serving as a negative reinforcer, thereby increasing abstinent behavior.

Evidence and Research. While some studies have demonstrated the ability of disulfiram treatment to help alcohol-dependent patients reduce their alcohol consumption (Laaksonen, Koski-Jannes, Salaspuro, Ahtinen, & Alho, 2008), a review of 24 studies revealed a surprising lack of evidence supporting the use of disulfiram (Hughes & Cook, 1997). In the early 1980s, for example, a highly influential trial showed no evidence that treatment with disulfiram improved abstinence rates or time to first drink. However, the results were clearly affected by the low treatment adherence rates (around 20%) associated with disulfiram therapy (Fuller et al., 1986). Because disulfiram does not help with cravings, patients can simply stop taking disulfiram on days when the urge to drink becomes overwhelming. Disulfiram administered in a supervised setting may be more successful in a subset of the alcohol-dependent population with longer histories of alcohol dependence (Diehl et al., 2010).

Formulation and Dosing. Disulfiram (Antabuse) is available in 250-mg and 500-mg oral tablets. The typical daily dose is 250 mg daily, with a range of 125 mg to 500 mg (the maximum approved daily dose). Disulfiram should not be started if alcohol has been consumed within the previous 12 hours.

Side Effects. Common side effects in abstinent patients include mild headache, skin rash, acne, drowsiness, fatigue, impotence, and a metallic taste in the mouth. Infrequently, disulfiram-induced hepatotoxicity can progress to liver failure, even in those without a prior history of liver problems. Hepatotoxicity risk peaks after 60 days of treatment and is usually reversible if disulfiram is stopped before the development of liver failure (Barth & Malcolm, 2010).

Contraindications and Safety. Disulfiram is contraindicated in patients with a history of severe cardiac or liver problems and those with previous allergic reactions to the medication.

Pregnancy. Disulfiram is classified as a Pregnancy Class C medication by the FDA (see "Alcohol dependence").

Other Medications

While this section has exclusively focused on medications that are FDA-approved for the treatment of alcoholism, others have also been shown to be of benefit. Baclofen, a $GABA_B$ receptor agonist, may be of particular benefit

in alcohol-dependent subjects with impaired liver functioning (Addolorato et al., 2007). Ondansetron, a 5-HT_3 antagonist, is particularly effective in those with an early onset of alcohol problems (Johnson et al., 2000). A multisite trial has also shown topiramate, which has actions at the $GABA_A$ and glutamate receptors, to be useful in the treatment of alcohol-dependence (Johnson et al., 2007).

Opioid Dependence: Antagonist Medications

Naltrexone

Naltrexone is an opioid receptor antagonist approved by the FDA for the treatment of both alcohol and opioid addiction.

History. In response to the rising drug experimentation and abuse of the 1960s, the Special Action Office for Drug Abuse Prevention (SAODAP) was created in 1971. The following year, Congress passed the Drug Abuse Office and Treatment Act which included, among its various provisions, a mandate to increase research funding for development of nonaddictive antagonist medications for heroin addiction (Julius, 1979). From this research, several compounds showed promise; EN-1639A (naltrexone) had the ideal characteristics for an outpatient medication for the treatment of opioid addiction. Naltrexone was made by modifying naloxone, a short-acting, intravenously delivered opioid antagonist that is used to treat opioid overdose. These modifications improved naltrexone's absorption when administered orally and significantly increased its duration of action (Resnick, Volavka, Freedman, & Thomas, 1974). In 1983, naltrexone was approved by the FDA for opioid addiction treatment in an oral tablet that is dosed daily. In 2010, the FDA approved a sustained-release, monthly intramuscular injectable formulation for the same indication.

Pharmacology. Naltrexone is a nonaddictive opioid receptor antagonist that competitively blocks the opioid receptor, preventing opioids from binding and subsequently blocking the euphoria and reinforcing effects of opioids (Coviello, Cornish, Lynch, Alterman, & O'Brien, 2010). By blocking the opioid-induced high, naltrexone presumably decreases or extinguishes opioid use (Rawson, Glazer, Callahan, & Liberman, 1979). Although naltrexone may help also reduce opioid cravings (Judson, Carney, & Goldstein, 1981), many patients have reported a minimal effect on craving.

Evidence and Research. The Heroin Antagonist and Learning Therapy (HALT) Project compared oral naltrexone therapy and behavioral treatments in opioid-addicted subjects and found that oral naltrexone, either with or without behavioral treatments, was highly effective in extinguishing

opioid-taking behaviors (Rawson et al., 1979). It has recently been reported that sustained-release naltrexone increases abstinence and treatment retention while reducing cravings and relapse risk (Gastfriend, 2011).

Formulation and Dosing, Side Effects, and Pregnancy. See "Alcohol dependence."

Contraindications and Safety. Naltrexone may inadvertently induce opioid withdrawal in patients who are actively using or have recently used opioids. Therefore, patients should only start on naltrexone after at least a week of abstinence. With longer acting opioids that are slow to be eliminated from the body, like methadone, the risk is even higher. Avoiding iatrogenic (physician-caused) withdrawal is especially important for patients who are contemplating treatment with the injectable, sustained-release formulation of naltrexone. In these patients, a persistent withdrawal state could emerge if sustained-release naltrexone is administered too early. The easiest way to assess risk of naltrexone-induced opioid withdrawal is by performing a challenge test. A patient is given a small dose of naloxone intravenously or naltrexone orally and observed for about half an hour for the emergence of any withdrawal symptoms. Absence of any withdrawal symptoms indicates that the patient is a good candidate to initiate naltrexone treatment.

Due to the risk of hepatotoxicity, naltrexone is contraindicated in patients with acute hepatitis or liver failure. Caution should be exercised in prescribing to patients with a history of current or past liver disease. As naltrexone and its main metabolite are primarily excreted in the urine, caution is also recommended when prescribing to patients with renal insufficiency.

Special Considerations: Treatment Adherence. Similar to the use of disulfiram for alcohol (see "Disulfiram"), the lack of patient adherence limits the efficacy of naltrexone. This may be due to naltrexone's general lack of efficacy at decreasing opioid craving, that is, patients taking naltrexone orally may not take their daily dose if they think they are going to use opioids in the near future. Thus, like disulfiram, oral naltrexone is widely believed to mostly benefit a subset of psychosocially stable and highly motivated patients, such as opioid-dependent healthcare professionals (van der Brink, Goppel, & von Ree, 2003). The sustained release formulation may be of additional benefit, as it is effective for a period of 4 weeks following a single intramuscular injection. Thus, patients do not have the option of suddenly discontinuing naltrexone when they want to return to using opioids. The injectable form of naltrexone increases treatment retention in opioid-addicted individuals (Comer et al., 2006). The improvement in retaining patients in substance abuse treatment is important as it sets the stage for other treatment interventions to be utilized, especially psychosocial and behavioral therapies (See Carroll & Kiluk, Chapter 12, this volume).

Opioid Dependence: Agonist Medications

Agonist medications stimulate the opioid receptor either completely (full agonists) or incompletely (partial agonists). The degree of agonism, or stimulation, of the receptor largely determines its physiological effects and clinical usefulness in treating opioid-addicted patients. Agonist therapy is generally considered to be most effective as a maintenance treatment rather than for only detoxification or short-term use.

Methadone

Methadone is a synthetic *full opioid agonist* that has been approved by the FDA for over 40 years. It is approved for maintenance treatment of opioid addiction, detoxification of opioid withdrawal symptoms, and for the treatment of severe pain.

History. German scientists originally developed methadone as a synthetic opioid in 1939 under the trade name Amidon. Following the end of World War II, the Allied nations took control over Germany's patents and research records. This led to the introduction of methadone to the U.S. market in 1947. Originally approved for its analgesic and cough-suppressing properties, it was not until the 1960s that methadone was investigated for treating opioid addiction.

Groundbreaking studies in the 1960s demonstrated that methadone maintenance treatment in heroin-dependent patients prevented withdrawal, did not produce euphoric effects like heroin, helped attenuate cravings, and enabled addicted patients to resume productive lives (Kreek, 2000). Methadone received approval for a new FDA indication of opioid addiction in the early 1970s. Strict regulations from several pieces of legislation in that decade, including the 1973 Methadone Control Act, established strict controls that highly regulated the dispensing of methadone to addicted patients in special opioid treatment programs. The Substance Abuse and Mental Health Services Administration certifies these methadone clinics, and they are registered with the Drug Enforcement Administration (DEA). The often-burdensome regulations have persisted to the present day.

Pharmacology. Methadone is an opioid medication with a long duration and slow onset of action. It is a full agonist at the opioid receptor (Kristensen, Christensen, & Christup, 1994). Stimulation of the opioid receptor is predominantly responsible for both the therapeutic and adverse effects of methadone, including analgesia, physical dependence, respiratory depression, constipation, pupillary constriction, and euphoria. The primary use of methadone in opioid-addicted patients is to reduce cravings in abstinent patients without producing the intense euphoric effects of heroin. In this

way, methadone is utilized as a maintenance medication to keep addicted patients from abusing opioids.

Methadone is administered orally and has a slower onset of action than intravenously administered heroin. As a consequence, it lacks an intense euphoric effect. In addition, a *cross-tolerance* develops between heroin (as well as other opioids) and methadone after chronic opioid use (Dumas & Pollack, 2008). "Cross tolerance" refers to the phenomenon whereby persistent use of an opioid agonist (e.g., heroin) results in physiological tolerance to many of the effects (including euphoria) of other members of the medication class (e.g., other opioids). For instance, a cross-tolerance occurs between all opioids including heroin, methadone, morphine, oxycodone, and hydrocodone.

Methadone also exhibits antagonism at the NMDA glutamate receptor (Ebert, Andersen, & Krogsgaard-Larsen, 1995). These properties may contribute to the ability of methadone to reduce cravings in opioid-addicted patients (Preston, Umbricht, & Epstein, 2000), as NMDA stimulation has been implicated in the development and evolution of various abstinence-related phenomenon, including cravings, withdrawal, and affective changes (Bisaga & Popik, 2000).

Research and Evidence. A large study showed a decrease in illicit opioid use with medium and high doses of methadone (up to 50 mg and 100 mg daily, respectively) as measured by negative urine drug screens and treatment adherence, with better success rates at higher doses (Strain, Bigelow, Liebson, & Stitzer, 1999). Additionally, a study of over 800 opioid-addicted individuals in methadone treatment demonstrated a lower rate of mortality among those who had continued in methadone maintenance versus those who had dropped out of or who had left treatment. This includes a remarkable 20% lower risk of death from unnatural causes, primarily heroin overdose (Fugelstad, Stenbacka, Leifman, Nylander, & Thiblin, 2007). Methadone also improves medical and social problems associated with the abuse of opioids. A meta-analysis investigating the effect of methadone on illicit opioid use, HIV risk behaviors, and drug-related criminal behavior revealed improvements in all three outcomes (Marsch, 1998).

Formulation and Dosing. Methadone (Dolophine) is available in 5- and 10-mg tablets and a cherry-flavored solution (Methadose) containing 10 mg of methadone per milliliter. Methadone tablets can be prescribed by physicians outside of methadone clinics for severe pain without any of the strict federal regulations, while Methadose is used exclusively for treatment of opioid addiction, and only in certified and registered methadone clinics. Methadone is generally started at 20–30 mg for the initial dose with another 5 or 10 mg dose several hours later if the patient is still experiencing significant withdrawal symptoms. The maximum cumulative dose on

the first day is 40 mg. Subsequent titration of methadone dose for maintenance therapy should be done gradually and cautiously due to its long duration of action and risk of overdose and death from respiratory depression if increased too rapidly. This risk is amplified in patients who may be concomitantly using central nervous system depressants such as alcohol or benzodiazepines. Typical effective daily maintenance doses are between 80 and 120 mg. Daily doses under 60 mg are less effective and may lead to poorer treatment retention rates than doses above 80 mg (Caplehorn & Bell, 1991). Some patients may require twice daily dosing of methadone due to break-through cravings from increased metabolism. These rapid metabolizers often need higher total daily doses as well (Adinoff, 2008).

Side Effects. Common side effects include constipation, nausea, vomiting, dizziness, drowsiness, dry mouth, headache, sweating, itching, lightheadedness, and weakness.

Safety and Contraindications. The foremost safety consideration is overdose with resultant respiratory depression and death. This is primarily a concern due to methadone's slow onset of action and slow elimination from the body, leading to an accumulation and overdose symptoms that may present in a delayed fashion. Methadone has also been associated with rare cases of serious cardiac arrhythmias (QT interval prolongation and torsade de pointes), typically with high doses administered multiple times daily (Krantz, Kutinsky, Robertson, & Mehler, 2003).

Pregnancy. Methadone is classified as a Pregnancy Class C medication by the FDA.

Buprenorphine

Buprenorphine is approved by the FDA for the treatment of opioid addiction. It works similarly to methadone but differs in its *partial* stimulation of the opioid receptor (Figure 11.5). In addition, practitioners are able to prescribe buprenorphine in outpatient office-based settings (that do not require DEA approval, as is required for methadone maintenance treatment).

History. Buprenorphine was developed in the United Kingdom and marketed as an analgesic medication beginning in 1978. The Drug Addiction Treatment Act of 2000 in the United States allowed opioid addiction treatment with certain opioid agonist medications to occur in an outpatient setting (rather than just methadone clinics). There were no medications that fit under the law until the FDA approved buprenorphine in 2002. Physicians are required to receive additional training to prescribe outpatient buprenorphine for addiction.

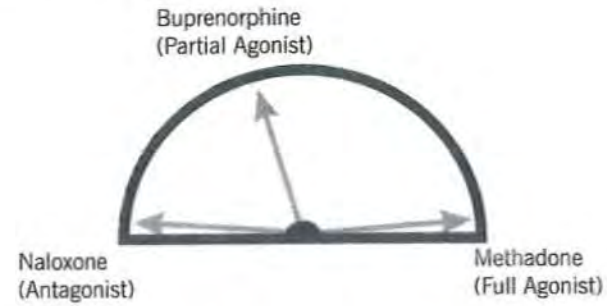

FIGURE 11.5. Pharmacology of therapeutic opiates. Compounds stimulate opiod receptors to different degrees. Methadone, a full agonist, activates opiod receptors to the highest degree. Naltrexone, an antagonist, turns the receptor completely off. Buprenorphine is a partial agonist and activates the receptor partially but not to the degree of a full agonist.

Pharmacology. Buprenorphine is an opioid with partial agonism of the opioid receptor. It is the partial agonism at the opioid receptor that is responsible for much of its unique clinical properties as a treatment for opioid addiction. As a partial agonist, buprenorphine incompletely stimulates the opioid receptor. This results in buprenorphine's ability to prevent or attenuate opioid withdrawal symptoms and cravings in abstinent opioid-addicted patients. At the same time, buprenorphine does not cause the highly reinforcing euphoric effects that full agonists (i.e., heroin or methadone) can cause, thus reducing the abuse potential (Jasinski, Pevnick, & Griffith, 1978). There is also a ceiling effect in its subjective effects on mood. That is, there is a plateauing of buprenorphine's subjective effects even with higher doses. The partial agonism at the opioid receptor and the ceiling effect are also thought to be responsible for the lower risk of respiratory depression and death in overdose compared with full agonist opioids (Robinson, 2002), demonstrating buprenorphine's strong safety profile and appropriateness for outpatient, office-based treatment (Walsh, Preston, Stitzer, Cone, & Bigelow, 1994). Buprenorphine has a relatively gradual onset of action and a long duration of action, which weakens the addictive potential and allows for dosing on a daily or even every-other-day schedule.

Research and Evidence. A large, multicenter study of outpatients revealed a dramatic improvement in the percentage of negative urine drug screens as well as decreased craving compared to placebo in the subjects treated with buprenorphine. In fact, the clinical trial ended early so that the patients receiving placebo could start taking buprenorphine (Fudala et al., 2003). A slow-release, subcutaneously implantable formulation of

buprenorphine that provides a steady amount of buprenorphine to the circulation for 6 months has been shown in early studies to increase negative urine drug screens, decrease cravings, and increase treatment retention by twofold over standard daily sublingual buprenorphine therapy (Ling et al., 2010). The extended-release formulation, not yet available for clinical use, may be especially useful in patients for whom treatment adherence has been an issue.

Formulation and Dosing. Buprenorphine comes in a tablet and in a film, both designed to disintegrate when placed under the tongue (sublingual). The tablet is available with buprenorphine only (Subutex) or in a combination (Suboxone) of buprenorphine and naloxone, the opioid receptor-blocking medication. The film is only available in the combination form. Subutex comes in 2-mg and 8-mg tablets. Suboxone has a 4:1 buprenorphine: naloxone ratio and is available in a 2-mg buprenorphine/0.5-mg naloxone tablet/film and an 8-mg buprenorphine/2-mg naloxone tablet/film. Naloxone helps prevent the intravenous injection of solubilized Suboxone tablets (see "Special Considerations: Diversion and Abuse" below).

Side Effects. Common side effects include drowsiness, dizziness, constipation, nausea, vomiting, diarrhea, abdominal discomfort, headache, sweating, weakness, flushing, and insomnia.

Safety and Contraindications. Buprenorphine is generally considered to be a safe medication for opioid addiction treatment due to its favorable side effect profile and the ceiling effect described above. Although there have been reports of deaths associated with buprenorphine, these primarily occur when buprenorphine tablets are ground up, solubilized, and intravenously injected. This is particularly dangerous when buprenorphine is injected concomitantly with benzodiazepines (Tracqui, Kintz, & Ludes, 1998). Therefore, caution should be exercised when prescribing buprenorphine to patients who are using central nervous system depressants such as benzodiazepines or alcohol.

When transitioning patients from methadone maintenance to buprenorphine it is important to avoid inducing acute withdrawal from methadone by starting buprenorphine too early. This is due to the precipitated withdrawal phenomenon that can occur when methadone's full agonist activity at the opioid receptor is blocked by buprenorphine's partial agonist activity, leading to a net decrease in opioid receptor stimulation. Patients on methadone maintenance should have their dose gradually tapered (due to methadone's slow excretion from the body) and buprenorphine should be started after the onset of some mild withdrawal symptoms have emerged, as this would indicate that methadone is no longer occupying most of the opioid receptors (Breen et al., 2003).

Pregnancy. Buprenorphine is classified as a Pregnancy Class C medication by the FDA.

Special Considerations: Opioid Agonist Therapy

Controversy

Since the early days of methadone maintenance therapy there has been controversy surrounding the use of opioid agonists for the treatment of opioid addiction (Brown, Jansen, & Bass, 1974). Critics have argued that maintenance therapy with either methadone or buprenorphine constitutes a substitution of one addiction for another. Thus, the argument is that addiction is never actually treated or cured; it is just transferred to a different addicting drug. However, agonist therapy now is considered not only a legitimate treatment for opioid addiction, but also one of the most effective treatments available. It enables patients to improve and recover their psychosocial functioning, health, and overall quality of life, as well as avoid many of the maladaptive behavioral patterns associated with opioid addiction. While a physical dependence remains, the primary symptoms of addiction (loss of control, compulsive use, and continued use despite adverse consequences) are subdued or completely ameliorated.

Medication Selection

Due to the stigma of using agonist medications, some patients and providers may be unwilling to consider methadone or buprenorphine as a treatment option. For these patients, naltrexone may be an appropriate choice, particularly the injectable, sustained-release version, in conjunction with psychosocial interventions. For those patients who are able and willing to take methadone or buprenorphine, the choice between the two for maintenance therapy often depends on individual characteristics and previous treatment experiences. Both medications are effective when used for short-term detoxification of acute withdrawal symptoms and for long-term maintenance therapy (Ahmadi, 2003; Bickel et al., 1988; Stimmel, Goldberg, Rotkopf, & Cohen, 1977). However, patients with more severe opioid addiction with strong cravings may do better with methadone treatment due to methadone's full agonist activity at the opioid receptor. In addition, the more highly structured environment of the methadone clinic may be beneficial to these patients. Similarly, methadone treatment may be indicated for individuals who have failed office-based buprenorphine treatment. On the other hand, patients with more stable psychosocial situations (e.g., housing, employment) may do well with buprenorphine on an outpatient basis, which has the added benefit of avoiding the stigma associated with methadone clinics.

Diversion and Abuse

As discussed previously, methadone is dispensed in a highly regulated fashion in special methadone clinics with direct observation of dosing by clinic staff. Thus, diversion and misuse is primarily a concern in patients allowed take-home doses of methadone for unsupervised administration. Rates of methadone diversion via intravenous injection in Australia revealed that more highly regulated methadone clinics (like those in the United States) had dramatically lower rates of diversion than less regulated ones. Rates of diversion were under 5% in the more highly regulated clinics versus over 60% at clinics that provided take-home doses (Ritter & Di Natale, 2005).

Given that buprenorphine is more often dosed in less regulated settings compared to methadone, there has been heightened concern of the potential for diversion and abuse. Even though buprenorphine tablets taken sublingually have not been shown to result in euphoric effects, ground up and intravenously administered buprenorphine has been theorized to increase its positive reinforcing effects enough to significantly increase its abuse potential (Sung & Conry, 2006). Buprenorphine abuse has been observed in Europe and other regions where buprenorphine is frequently prescribed without naloxone. Consequently, a formulation containing buprenorphine and the opioid receptor antagonist naloxone was released in the United States as Suboxone. The rationale for including naloxone is based on the theorized ability of naloxone to block the effects of buprenorphine and/or cause unpleasant withdrawal symptoms when the medication is injected intravenously, thus decreasing its abuse liability. Some 80% of intravenous heroin abusers reported having a bad experience when injecting solubilized Suboxone but not with buprenorphine alone (Alho, Sinclair, Vuori, & Holopainen, 2007). Because of naloxone's poor sublingual absorption, it typically is not absorbed when Suboxone tablets are taken sublingually. Little diversion of the combined buprenorphine and naloxone exists, which is the form used widely in most of the United States. When diversion does occur, it is primarily used by addicted patients for the self-medication of withdrawal symptoms rather than for intoxication or euphoria (Mitchell et al., 2009). In fact, opioid-addicted subjects were less likely to report subjective reinforcing effects from buprenorphine combined with naloxone (taken sublingually as directed) than from buprenorphine alone or from heroin (Comer et al., 2010).

Pregnancy

Pregnant women who are addicted to opioids comprise a high-risk population. Opioid abuse during pregnancy increases the risk of obstetrical and medical complications for both the mother and the fetus. Bringing women into substance abuse treatment improves both maternal and fetal outcomes (Kaltenbach & Berghella, 1998). Detoxification from opioids while

pregnant is widely discouraged due to concerns of risk to the fetus caused by *in utero* opioid withdrawal. In addition, the risk of relapse in pregnant women is exceedingly high even if detoxification is successful. Thus, methadone maintenance has been widely considered the treatment of choice for opioid-addicted women during pregnancy (Kandall, Doberczak, Jantunen, & Stein, 1999).

One of the frequent consequences in neonates born of methadone maintained women is neonatal abstinence syndrome (NAS). This is an opioid-withdrawal syndrome in the newborns due to their development of physical dependence on methadone during gestation. NAS usually requires care in a neonatal intensive care unit for several days or more and detoxification with opioids (such as morphine drops). NAS is associated with developmental delay in the first year of life, but children tend to reach normative levels of functioning by age 2 (McCance-Katz, 1991).

Buprenorphine is both safe and effective in pregnant women (Johnson, Jones, & Fischer, 2003). In fact, neonates of buprenorphine-treated women, relative to those women treated with methadone, have almost half the incidence of NAS and require less morphine for fewer days for the treatment of NAS. They also have shorter hospital stays than methadone-treated women (Jones et al., 2010; Kakko, Heilig, & Sarman, 2008).

Adolescents

Abuse of opioids, especially pain medications like hydrocodone and oxycodone, has been an increasingly common problem in the adolescent population; an epidemiological survey of 12th-grade students in the United States found that opioid pain medication abuse was the second most frequently abused substance after marijuana (Compton & Volkow, 2006). Treatment for this patient population has typically involved buprenorphine rather than methadone, largely due to the highly regulated and controlled nature of methadone clinics. Under the Panini State Methadone Maintenance Treatment Guidelines of 1992, methadone maintenance in the United States is only allowed in adolescents after they have failed at least two attempts of detoxification or rehabilitation treatment (Simkin & Grenoble, 2010). Adolescents treated with buprenorphine for withdrawal, relative to those treated with clonidine, have fewer withdrawal symptoms, more negative urine drug screens, decreased HIV-risk behavior, and are more likely to remain in treatment (Marsch et al., 2005). Opioid-addicted adolescents undergoing a 12-week maintenance period on buprenorphine, compared to a 2-week detoxification period, resulted in decreased overall opioid use, intravenous substance administration, and use of other drugs (Woody et al., 2008). These studies support the use of maintenance buprenorphine treatment in adolescents.

Prescription Opioid Addiction

Abuse and addiction to prescription opioids has become increasingly problematic over the past decade for not just adolescents, but the general population as well. In treatment with buprenorphine in an outpatient-based setting, prescription opioid-addicted individuals treated with buprenorphine tended to stay in treatment longer and have more opioid-negative urine drug screens than those who were not on maintenance therapy. Buprenorphine may be a good option for this population (Moore et al., 2007).

Stimulant Dependence

Although there are currently no FDA-approved medications for the treatment of stimulant addiction, numerous medications have been investigated for their potential utility in treating individuals addicted to cocaine or methamphetamine. Current research in stimulant addiction has focused on the dopamine, GABA, glutamate, and serotonin systems as well as immunological therapies (Ross & Peselow, 2009). Studies of antiepileptics (carbamazepine, phenytoin), dopamine agonists (bromocriptine), amantadine, antidepressants (fluoxetine, desipramine, imipramine, bupropion), and naltrexone were reviewed in 2002 and none were considered effective in treating cocaine addiction (Silva de Lima, de Oliveira Soares, Reisser, & Farrell, 2002). Disulfiram, the cocaine vaccine, modafinil, vigabatrin, D-cycloserine, and topiramate have shown promise for the development of cocaine addiction treatments (Kampman, 2010; Price et al., 2009). Inconclusive findings have been reported on the efficacy of various other medications, including risperidone, imipramine, and amlodipine in the treatment of methamphetamine addiction (Meredith, Jaffe, Ang-Lee, & Saxon, 2005). Some of the more promising medications will be reviewed.

Disulfiram

Disulfiram has shown promise in treating cocaine addiction separately or in conjunction with coexisting alcohol dependence (Carroll et al., 2004). Individuals with alcohol and cocaine addiction who are taking disulfiram, in combination with naltrexone or alone, were more likely to be abstinent from both cocaine and alcohol compared to those taking a placebo (Pettinati et al., 2008). However, a Cochrane systematic review of disulfiram studies did not find clear evidence of its efficacy for treatment of cocaine addiction (Pani et al., 2010). Disulfiram may attenuate the reinforcing euphoric properties of cocaine (Baker, Jatlow, & McCance-Katz, 2007), decrease craving, and increase the dysphoric effects of cocaine (Haile, Kosten, & Kosten, 2009). In addition to blocking the enzyme acetaldehyde dehydrogenase (see "Alcohol"), disulfiram also blocks the enzyme dopamine beta-hydroxylase.

This enzyme converts dopamine to norepinephrine. Treatment with disulfiram then leads to increased dopamine levels, which may be responsible for its beneficial effects in the treatment of cocaine addiction (Petrakis et al., 2000).

Cocaine Vaccine

Another promising treatment for cocaine addiction is the development of a vaccine that stimulates production of antibodies directed against cocaine. These anticocaine antibodies bind to cocaine molecules and make the antibody–cocaine complex too large to cross the blood–brain barrier. Binding cocaine with antibodies makes cocaine unable to affect brain reward pathways and limits its other damaging physiological effects throughout the body (Sofuoglu & Kosten, 2006). Cocaine vaccines are currently being developed and one has now progressed to clinical trials (Kinsey, Kosten, & Orson, 2010). The safety of this vaccine and its ability to effectively stimulate cocaine-directed antibodies has been established (Kosten et al., 2002). The vaccine has also been shown to decrease cocaine self-administration in animal models of addiction (Fox et al., 1996) as well as to attenuate the euphoric effects of cocaine and decrease cocaine use in individuals addicted to cocaine (Martell, Mitchell, Poling, Gonsai, & Kosten, 2005; Martell et al., 2009).

Modafinil

Modafinil (Provigil) is a nonstimulant medication approved by the FDA for the treatment of the sleep disorder narcolepsy. Modafinil is believed to modulate the dopamine, GABA, and glutamate systems among others, and has been shown in some studies to reduce cocaine cravings and increase abstinence rates (Martinez-Raga, Knecht, & Cepeda, 2008).

Bupropion

Bupropion is a norepinephrine and dopamine reuptake-inhibiting medication that is FDA-approved for the treatment of major depression and nicotine dependence. It has been demonstrated to decrease subjective reinforcing effects and cue-induced cravings in methamphetamine-addicted individuals (Newton, De La Garza, Kalechstein, Tziortzis, & Jacobsen, 2009). Bupropion, in conjunction with behavioral therapies, was reported to increase abstinence in patients with low to moderate degrees of methamphetamine addiction (Elkashef et al., 2006). In other studies, however, bupropion was no more effective than placebo in reducing methamphetamine use (Shoptaw et al., 2008).

Modafinil

Modafinil, in addition to its potential for cocaine addiction treatment, has also been studied for the treatment of methamphetamine addiction. Although no differences were found between modafinil and placebo in abstinence rates, cravings, or severity of dependence in methamphetamine-addicted subjects, medication-adherent subjects did provide more negative urine drug screens (Shearer et al., 2009).

Cannabis Dependence

There are no FDA-approved medications for the treatment of cannabis addiction. Various medications have been studied, including tetrahydrocannabinol (THC), nefazodone, bupropion, divalproex, and naltrexone. Most of these have not been shown to be effective in treating cannabis addiction with the exception of THC, the active ingredient in cannabis, which has shown some promise (Budney, Roffman, Stephens, & Walker, 2007).

Conclusion and Future Directions

The past two decades have seen dramatic advances in the pharmacological treatment of substance use disorders. As described in this chapter, the use of oral naltrexone for alcohol dependence, the new formulation of extended-release naltrexone for both alcohol and opioid dependence, acamprosate for alcohol dependence, and buprenorphine for opioid withdrawal and maintenance have all greatly benefitted treatment outcomes in addicted individuals. Nevertheless, medications for addiction treatment remain significantly underutilized. Concerns regarding cost, differing philosophical approaches to treatment, availability, and the absence of the resources necessary for prescribing and dispensing medication have limited the use of these pharmacological approaches. Fortunately, the situation is gradually improving as the benefits of pharmacological intervention in this patient population have become increasingly evident. Physician involvement in addiction treatment has become more widespread and some medications (e.g., opioid agonists) have become more accessible.

An additional factor in the enhanced use of medications for substance abuse is the heightened awareness of the benefits that accrue from combining pharmacotherapy with psychosocial treatments and support groups. Substance abuse is a chronic disease, and medications for any chronic disease, of course, are not a panacea. Limited success is expected in a substance-abusing individual with medications alone in the absence of other behavioral interventions, in much the same way as one would expect limited

success from cardiac rehabilitation in a patient who persists in smoking. Medications, behavioral treatments, and support groups all potentiate each other's beneficial effects in the treatment of substance abuse when used in combination. Thus, maximizing treatment outcomes requires rigorous attention to all aspects of recovery.

Despite impressive advances in pharmacological treatments, there are some noteworthy disappointments. To date, there are no FDA-approved medications for the treatment of cocaine, amphetamine, or cannabis dependence and none appear to be on the near horizon. This is not for lack of trying. Several medications have proven successful in decreasing stimulant use in both animal studies and open label trials (when the individual knows what pill he or she is taking) only to later show disappointing outcomes in a "gold standard" double-blind, placebo-controlled clinical trial. In the face of this disappointment, however, dramatic progress has been made in understanding the neurobiology underlying the development and persistence of addictive disorders. Although the translation from the laboratory to the clinical setting is difficult, these achievements are certain to yield concrete benefits over time.

Advances in our understanding of the neurobiology of substance abuse may require a more sophisticated assessment of the addicted individual. Some medications may be more effective for those with specific genetic backgrounds. For instance, alcohol-dependent patients with a variant of the opioid receptor (OPRM1) are far more responsive to naltrexone than those with a different OPRM1 gene (Anton et al., 2008; Oslin et al., 2003). In addition, brain scans may identify a specific neural circuit or receptor configuration that is particularly responsive to a specific medication or even a combination of medications. Although similar claims have been made since genetic testing and brain-imaging techniques have become available, the ease of obtaining a full-gene analysis and the stunning improvements in measuring brain functioning suggest that these promises are closer to fruition. At this time, however, there is no scientific evidence supporting the use of brain imaging to either diagnose or advise treatment approaches for substance abuse (Adinoff & Devous, 2010; Leuchter, 2009).

An important caveat to this optimism is warranted, however. Many medications used to treat addictive disorders lack sufficient (or any!) evidence that they are, in fact, beneficial. Surprisingly, many of the medications commonly used to treat cocaine and amphetamine have even been shown to be ineffective. The dangers inherent in this approach include inducing unrealistic expectations from the patient and the treatment team as well as exposing a patient to potential side effects from a medication that offers little likelihood of benefit. Furthermore, these medications may be quite expensive yet yield no benefit except to the company claiming a presumed cure for addiction. Recent examples of expensive treatments without scientific support include Prometa (a combination of hydroxyzine [an

antihistamine], flumazenil [a benzodiazepine antagonist], and gabapentin) for alcohol, cocaine, or opioid addiction and rapid detoxification for opioid withdrawal (Collins, Kleber, Whittington, & Heitler, 2005; Pfab, Pfab, Hirtl, & Zilker, 1999). When the time comes that we can prescribe safe and effective medications specific to a person's own genetic and biologic profile, an additional benefit will likely be evident. This medicalization of substance use disorders will clearly demonstrate the inherent neurobiological basis of substance abuse and will significantly diminish the social stigma commonly associated with this disease.

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