

## Biological Basis of Drug Addiction

---

TONY P. GEORGE

*Yale University School of Medicine and Connecticut Mental Health Center, New Haven, Connecticut, U.S.A.*

### I. INTRODUCTION

Drug abuse and dependence constitute a major public health problem in the United States. The consequences of licit (e.g., alcohol and nicotine) and illicit (e.g., cocaine, heroin, marijuana, phencyclidine) drug use leads to significant medical morbidity, mortality, and health care expenditure, and contributes to significant personal, family, and social misfortune. It is estimated that drug addiction costs U.S. society ~\$67 billion each year in terms of crime, lost job productivity, and other social problems [1]. However, drug addiction continues to be both underrecognized and undertreated by primary care physicians and psychiatrists. This is particularly unfortunate since there are several very effective treatments for alcohol, opioid, and nicotine dependence disorders, especially when combined with appropriate psychosocial interventions (e.g., Alcoholics Anonymous, drug counseling, smoking cessation counseling). The belief among health care providers that drug addiction is a "moral failing" or "bad habit" is, unfortunately, still a common one, and it is well appreciated that many physicians (including psychiatrists) take a stance of "therapeutic nihilism" with respect to treatment of individuals with drug addiction. However, there is increasing evidence that addictive disorders have a strong biological basis, and this knowledge will most likely lead to effective treatments

for all addictive disorders, including those that do not currently have effective pharmacotherapies such as cocaine and methamphetamine addiction [2]. The purpose of this chapter is to delineate the biological underpinnings of drug addiction, and to describe current and future biological treatment approaches for these disorders based on such knowledge.

### II. DEFINITIONS: DRUG ABUSE, DEPENDENCE AND ADDICTION:

It is important to clearly define common terms that are used to describe drug-seeking behaviors, and the functional consequences of drug misuse syndromes, since these terms have specific connotations, and should not be used interchangeably. Drug *abuse*, according to the DSM-IV [3], refers use of a psychoactive substance that leads to impairment of social and/or occupational functioning as evidenced by one of: (1) use of the drug under hazardous circumstances (e.g., driving a car); (2) drug use leads to neglect of external obligations (e.g., intoxicated and then forgets to pick up their child from daycare); (3) legal problems arising from drug use (e.g., driving under the influence [DUI] conviction); (4) interpersonal problems related to persistent drug use (e.g., loss of job, divorce). The above-referred mnemonic ("h-e-l-p") is useful for remembering the four com-

ponents that contribute to the diagnosis of drug *abuse* disorders. In contrast, drug *dependence* describes a constellation physiological adaptations (e.g., tolerance and withdrawal) and functional consequences of such physiological adaptation (drug taken in larger amounts, and for longer than intended, social and occupation activities impaired by drug use). It is important to note that the terms abuse and dependence are not mutually exclusive when describing drug use disorders, and it is possibly to be diagnosed with one, both, or neither diagnosis when classifying drug use. Finally, drug *addiction* refers to compulsive drug-seeking, loss of control, and the adverse social and occupational consequences related to use of drugs of abuse.

### III. NEURAL SUBSTRATES OF DRUG ADDICTION

#### A. Summary of Receptor Site(s) of Action of Drugs of Abuse

Table 1 describes the major classes of drugs of abuse, their purported site(s) of action at the molecular level, and the endogenous neurotransmitters that appear to mediate their actions. One common mechanism of all addictive drugs is their ability to increase dopamine (DA) release and turnover in the mesolimbic ("reward") pathway (Fig. 1). In fact, there is increasing evidence for afferent regulation of mesolimbic DA neurons by most other major central neurotransmitter systems including serotonin, GABA, glutamate, endogenous opioid peptide, and nicotinic cholinergic systems [2].

#### B. Mesolimbic DA System

A number of studies over the past 25 years have suggested that mesolimbic DA neurons, which project from the ventral tegmental area (VTA) in the mid-brain to the anterior forebrain nucleus accumbens (NAS) mediate the reinforcing effects of drugs of abuse (Fig. 1). This is suggested by experiments involving lesions to the VTA by mechanical (e.g., electrolytic), chemical (6-hydroxydopamine, kainic acid) methods that have implicated the involvement of this pathway in drug reward [4]. However, the normal function of the mesolimbic DA system seems to relate to forming relevant associations between salient and arousing chemical and behavioral stimuli (e.g., food, sex, stress) and internal rewarding or aversive states.

Thus, this system helps the organism acquire behaviors reinforced by both natural rewards and drug stimuli. It is thought that the activity of mesolimbic DA neurons normally habituates with repeated exposure [5,6]. However, drugs of abuse abort this habituation leading to a change in the set point of the mesolimbic DA system [7], which may underlie addictive behaviors.

#### C. Endogenous Opioid Peptide Reward Pathways

There is increasing evidence for afferent regulation of mesolimbic DA pathways by EOP systems. In addition, it appears that  $\mu$ - and  $\kappa$ -opioid systems have opposing actions on mesolimbic DA neurons, with stimulation of  $\mu$ -receptors (in the VTA) increasing DA release, and stimulation of  $\kappa$ -receptors (in the NAS) inhibiting DA release [8]. There is good neuroanatomic and function evidence for this interaction of opioid and DA systems at the level of the VTA [9]. In addition, recent studies suggest that EOP regulation of central DA pathways extends to tuberoinfundibular [10] and mesocortical DA pathways [11].

Besides mediating the reinforcing effects of opioid drugs, there is evidence from preclinical and clinical studies for EOP involvement in the reinforcing actions of other drugs of abuse, including alcohol [12-14], cocaine [15,16], methamphetamine [17], and nicotine [11,12]. These effects may ultimately be mediated through the DA reward system, given the afferent regulation of these DA neurons by opioidergic systems.

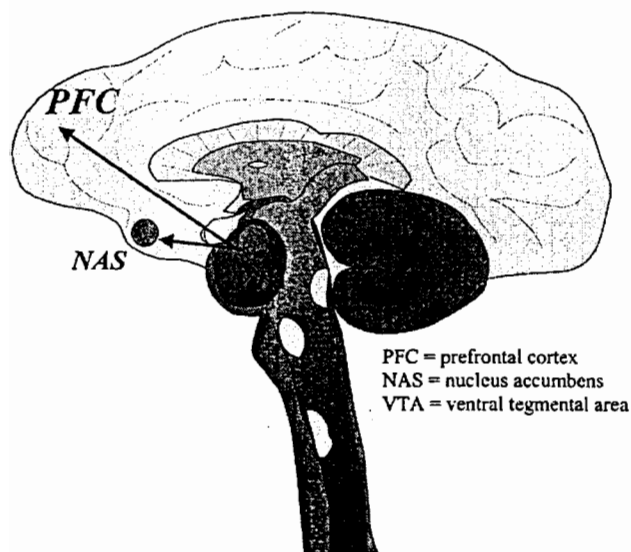
#### D. Hypothalamic-Pituitary-Adrenal (HPA) Axis

Evidence from animal and human studies indicates that environmental stress appears to be an important factor in drug relapse, and successful drug addiction treatment involves helping patients cope and address life stressors that inexorably lead to relapse. Numerous preclinical studies have documented that physical (e.g., footshock, restraint stress) and psychological (e.g., cue-induced) stressors can cause drug use reinstatement [16], and that stressors can lead to drug craving behaviors in human addicts [18]. In fact, increased cortisol (or corticosterone in rats) levels are known to potentiate the mesolimbic DA system, and may be a basis for stress-induced drug craving [16].

**Table 1** Site(s) of Action of Various Drugs of Abuse and Neurotransmitters Implicated in Their Actions<sup>a</sup>

Drug	Site of action	Endogenous neurotransmitter systems	Pharmacologic treatments
Alcohol/sedatives	Nonspecific membrane effects NMDA receptors (noncompetitive site) GABA <sub>A</sub> receptors (chloride channels) Voltage-dependent calcium channels	Glutamate GABA Dopamine Serotonin Endogenous opioids	Disulfiram Naltrexone Acamprosate SSRIs
Cocaine	Dopamine transporter (DAT) Norepinephrine transporter (NET) Serotonin transporter (SERT)	Dopamine Norepinephrine Serotonin GABA Glutamate Endogenous opioids	No proven pharmacotherapy Desipramine (and other TCAs) Dopamine Agonists, Disulfiram
Opioids	μ-Opioid receptors (e.g., morphine, heroin)	Endogenous opioids Dopamine Glutamate	Methadone Clonidine Naltrexone Buprenorphine
Marijuana	Cannabinoid (CB1, CB2) receptors	Anandamide Dopamine Endogenous opioids	No proven pharmacotherapy
Nicotine (tobacco)	Nicotinic acetylcholine receptors  ? Monoamine oxidase (A/B isoforms)	Acetylcholine  Dopamine Serotonin Norepinephrine GABA Glutamate Endogenous opioids	Nicotine Replacement (patch, gum, inhaler, spray) Sustained-Release Bupropion
Amphetamine	Vesicular monoamine transporter (VMAT) Monoamine transporter (DA, 5HT, NE)	Dopamine Serotonin Norepinephrine	No proven pharmacotherapy
Phencyclidine	NMDA receptors Dopamine transporter (DAT)	Glutamate Dopamine	No proven pharmacotherapy
MDMA (Ecstasy)	Serotonin transporter (SERT) Serotonin synthesis	Serotonin	No proven pharmacotherapy

<sup>a</sup>Examples of pharmacological agents which have been devised for use in the treatment of these drug abuse disorders are also given.



**Figure 1** Mesolimbic dopamine ("reward") pathways. The dopaminergic projections from the ventral tegmental area (VTA) to the nucleus accumbens (NAS) and prefrontal cortex (PFC) are diagrammed.

### E. Pharmacokinetics of Addictive Drugs: Implications for Drug Reward

There is substantial evidence that the rewarding effects of drugs of abuse correlate with how much drug gets into the brain and how quickly the drug reaches the brain. That is, in pharmacokinetic studies, both the drug level obtained and the rate of rise (e.g., ascending portion of curve) are important factors in predicting drug "liking" and "rewarding" effects. An example of cocaine pharmacokinetics with administration of cocaine by various routes, as assessed by plasma cocaine levels (in arbitrary units) over time after cocaine administration [19], is presented in Figure 2.

Oral cocaine (A) administration (e.g., chewing coca leaves) leads to very slow absorption of cocaine hydrochloride, which is a charged molecule that does not easily cross the mucous membranes. Consequently, the reported drug "high" is modest. Intranasal (i.e., snorted) cocaine (B) has a slightly faster rate of absorption and therefore produces more drug "high" than orally ingested cocaine. Finally, intravenous and free-base (crack) uses of cocaine (C) have much faster rates of absorption (in the first case due to an intravenous bolus of cocaine which gets to the brain in large amounts; in the second case because freebase cocaine is more membrane permeable and is rapidly absorbed through the pulmonary circulation and into the brain),

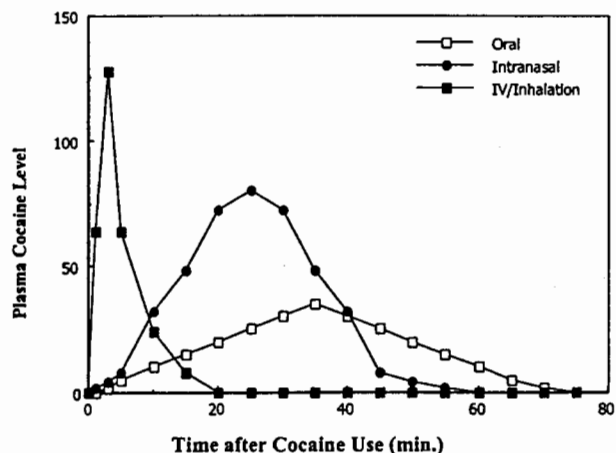
which correlate with a profoundly enhanced cocaine "high" compared to oral and intranasal routes. Interestingly, in controlled animal studies, the correlations between plasma levels of cocaine and reinforcing effects are not exact, and this may relate to differential tolerance with intravenous versus oral administration and differences in metabolite profiles produced by these two routes of cocaine administration [20].

## IV. BIOLOGICAL THEORIES TO EXPLAIN COMPULSIVE DRUG USE

There are several current and seemingly contradictory theories regarding the development of compulsive drug-seeking behavior and ultimately drug addiction [4,7,21–23]. Several aspects of these theories are compatible with the clinical course of addictive disorders and the disagreements between the theories relate to the complexities of drug addiction and the biochemical, neuroendocrine behavioral models in preclinical studies on which these theories are based.

### A. Allostatic Dysregulation Model

This theory of drug addiction has been proposed by Koob and LeMoal [7,21]. Allostasis refers to the counteradaptive changes in brain function induced by



**Figure 2** Pharmacokinetics of cocaine administration by three routes. The plasma concentrations of cocaine (in arbitrary units) produced by three routes of cocaine administration (oral, intranasal, and intravenous/inhalation) are depicted. The rewarding effects of cocaine and other drugs of abuse relate to how rapidly the drug enters the brain, which directly correlates with plasma drug levels.

chronic drug administration, such that there is a chronic deviation of the brain reward “set point,” which relates to reward circuit dysregulation. The brain circuits involved are presumably in the corticostriathalamic loop [24]. They describe a cycle of “spiraling distress” whereby alternating binge intoxication (with resultant drug tolerance) and negative affect associated with acute drug withdrawal leads to adaptive changes in brain reward mechanisms (e.g., the mesolimbic dopamine pathway, endogenous opioid systems) that consequently produce compensatory compulsive drug-seeking behavior, leading to the classical impairments in social and occupational functioning that constitutes drug addiction. Environmental stressors are seen as an important cofactor in both initiation and perpetuation of this cycle, presumably through alterations in HPA axis function [16]. As such, this view focuses on the positive (drug-liking) and negative (drug withdrawal) aspects of drug addiction, which are both processes that occur in the short term and lead to a dysregulation of “hedonic homeostasis.”

### **B. Incentive-Sensitization Model**

This theory, proposed by Berridge and Robinson [22], purports that like the allostatic model, chronic drug use leads to changes in reward system function, such that an addict becomes sensitized to drug use, but that these brain systems do not mediate euphoric effects of drug use (e.g., drug liking) but mediate a specific component of drug reward (“drug wanting”), which they refer to as “incentive salience.” This view of drug addiction, in contrast, is not based on short-term drug reward and withdrawal syndromes to explain the process of addictive behaviors, and may in fact be compatible with the observations that many drug users who achieve initial abstinence often relapse to drug use in the context of exposure to environmental cues that potentiate drug “wanting,” which is dissociable from drug “liking” [22]. Experimental support for the “incentive sensitization” model comes from recent functional neuroimaging studies in cocaine addicts [25] which demonstrated that the nucleus accumbens showed increases in blood flow (activation) during craving for cocaine, and not during acute intravenous administration.

### **C. Phasic/Tonic DA Release Model**

This model of drug addiction, posited by Grace [23], was first formulated in the context of understanding

how dysregulated dopamine dynamics may mediate the symptoms of schizophrenia [26]. It suggests that the mesolimbocortical dopamine system is dysregulated by chronic drug administration and that this dysregulation leads to drug addiction. Functionally, mesolimbic DA neurons have two types of activity: (1) tonic DA release, which is mediated by cortical glutamatergic afferents that ensures an appropriate basal level of mesolimbic DA activity; and (2) phasic DA release, which refers to evoked DA release, and is typically the type of DA activity stimulated by drugs of abuse like cocaine, amphetamine, and nicotine that leads to a large increase in synaptic DA levels. Of note, mesolimbic DA neurons have release-inhibiting preterminal DA autoreceptors ( $D_2$ ) that normally function to shut down mesolimbic DA neuron function when synaptic DA levels are excessive. With chronic drug exposure, tonic DA levels would be expected to rise, causing enhanced presynaptic DA autoreceptor stimulation, thus inhibiting mesolimbic DA neuron activity. Accordingly, the experience drug user will take drugs to offset this dysregulation in tonic DA release in an attempt to augment the diminished phasic DA release that is counteracted by increased tonic DA levels. This model assumes that the mesolimbic DA system is the unitary biological substrate of drug addiction, and is similar in concept to the allostatic state proposed by Koob and LeMoal [7,21].

### **D. Cognitive Deficits Model**

The prefrontal cortex is important in regulation of judgment, planning, and other executive functions, and it sends inhibitory projections to subcortical areas, which include the mesolimbic DA reward pathway. This model posits that: (1) individuals who develop addictive disorders have preexisting cognitive (e.g., prefrontal cortical) deficits that predispose them to impulsivity and compulsive drug-seeking behavior [27,28]; and (2) continued drug use further worsens the severity of these deficits through chronic and repeated insults to the prefrontal cortex [24]. For example, it is known that cocaine addicts have cerebral cortical perfusion deficits [28]. Such abnormalities in the “frontostriatal loop” are believed to contribute to impulsivity, compulsive drug-seeking behavior, and loss of behavioral control, which are associated with frontal cortical cognitive deficits and may explain the increasing severity of drug addiction with chronic and persistent drug use, especially in individuals with known deficits in PFC function (e.g., schizophrenia, antisocial personality disorder).

## V. MECHANISMS OF ADDICTIVE DRUG ACTION

### A. Cocaine and Psychostimulants

The monoamine transporter proteins, which act as a reuptake mechanism for terminating synaptic monoaminergic neurotransmission, are the primary site(s) of cocaine's action in the brain. Cocaine inhibits the reuptake of monoamine transmitters, in the order: dopamine (DA) > norepinephrine (NE) > serotonin (5-hydroxytryptamine; 5HT). Accordingly, cocaine administration leads to a massive elevation of synaptic monoamine levels [29]. DA is thought to be the most important neurotransmitter relevant to the reinforcing effects of cocaine, and DA agonists and antagonists have been tested as potential pharmacotherapies based on this putative mechanism. With repeated cocaine administration, a constellation of changes in brain function are induced, including in levels of postsynaptic receptors (e.g., downregulation of DA-D<sub>2</sub> receptors) and in second-messenger systems (e.g., cyclic-AMP response element binding protein [CREB], neurotrophins, [30]), which may explain some of the long-term clinical effects of chronic cocaine administration such as tolerance, withdrawal, and sensitization [31].

Psychostimulants (including methamphetamine, methylphenidate, and congeners) work primarily by releasing monoamines (DA, NE, 5HT) from presynaptic nerve terminals by two mechanisms: (1) blocking the vesicular monoamine transporter (VMAT), which sequesters monoamines in presynaptic vesicles, leading to increased levels of presynaptic free monoamines; and (2) reversing transport through monoamine transporter proteins (probably a consequence of #1). This leads to massive elevation of synaptic monoamine levels, the most important being DA. While the molecular mechanisms of psychostimulant drugs other than cocaine have received less study, there appear to be similar chronic adaptations in neural systems involved [22,32].

### B. Alcohol and Sedative Hypnotic Drugs

A discussion of the mechanisms of action of alcohol is given in Chapter 38 ("Biological Basis of Alcoholism"). Sedative-hypnotic agents like barbiturates (e.g., phenobarbital, secobarbital) appear to work through mechanisms in common with alcohol, including facilitation of GABA<sub>A</sub>-linked chloride ion transients (leading to target membrane hyperpolariza-

tion and reduced firing rates). The role of GABA-ergic and glutamatergic systems in mediating the effects of sedative-hypnotic drugs is becoming clearer [7], especially in light of the observation that benzodiazepines and related agents inhibit mesolimbic DA release (through stimulation of GABA-ergic afferent inputs onto these DA neurons).

### C. Nicotine and Tobacco

Nicotine is the primary constituent of tobacco products that appears to be responsible for the reinforcing effects of tobacco use [33]. The most common method of nicotine delivery is through smoking cigarettes. The primary site of action of nicotine is the nicotinic acetylcholine receptor (nAChR). The nAChR is a heteromeric ion channel complex that is composed of combinations of two  $\alpha$  ( $\alpha$ 2-9) and three  $\beta$  ( $\beta$ 2-4) subunits, with the  $\alpha$ 4 $\beta$ 2 nAChR being the predominant subunit complex in human brain [34]. The main ions that permeate this channel are sodium (Na<sup>+</sup>) and calcium (Ca<sup>2+</sup>), leading to neuronal membrane depolarization. Autoradiographic and immunocytochemical studies have demonstrated that nAChRs are located presynaptically on numerous neurotransmitter secreting neurons [34,35], including those for DA, NE, 5HT, GABA, glutamate, and EOPs, and stimulation of these receptors by nicotine leads to release of these transmitters. In contrast to other agonist drugs, after nicotine stimulates the nAChR, the receptor desensitizes almost immediately, and this progresses to nAChR inactivation. With repeated nicotine administration (as is the case with habitual smoking), this leads to a compensatory upregulation of nAChRs, known as the "paradoxical upregulation" of nAChRs by nicotine. This phenomenon may explain why dependent smokers find that the most satisfying cigarette of the day is the first one, and why nicotine cravings and withdrawals are so intense in the majority of dependent smokers. Animal models of nicotine dependence suggest that it takes 2-3 weeks for upregulated nAChR levels to return to normal after cessation of nicotine administration. Such a change in nAChR number and function is consistent with an allostatic alteration in these systems induced by repeated nicotine administration [7,21].

There is recent evidence from in vitro and positron emission tomography (PET) studies to suggest that an unidentified component of tobacco smoke (not nicotine) inhibits monoamine oxidase A (5HT) and B (DA, NE) isoforms, which are responsible for the degrada-

tion of monoamines. This additional action of tobacco may contribute to its psychopharmacologic properties [36,37].

#### D. Opioids

All opioid drugs work through agonism at the  $\mu$ -opioid receptor, at which the enkephalin subclass of endogenous opioid peptides (EOPs) are the endogenous neurotransmitters for these receptor systems. Full  $\mu$ -receptor agonist drugs include morphine, heroin (a morphine pro-drug), oxycodone, and methadone, and binding of opioid drugs to the  $\mu$ -receptor leads to activation of cAMP systems and inhibition of an outwardly rectifying  $K^+$  current, leading the membrane hyperpolarization [31,32]. Most addictive opioids are short acting (e.g., morphine, heroin, oxycodone), and long-acting preparations (e.g., methadone) have been used to treat opioid addiction using long-term maintenance (e.g., methadone maintenance). Most recently, partial  $\mu$ -receptor agonists (mixed agonist-antagonists) such as buprenorphine (which also has  $\kappa$ -antagonist properties, which presumably augments mesolimbic DA function) have shown effectiveness for the treatment of opioid dependence and addiction. In addition, there is good evidence that long-acting  $\mu$ -opioid antagonists (e.g., naltrexone) can be useful as a relapse prevention pharmacotherapy for opioid dependence.

#### E. Cannabinoids

Cannabinoids are plant alkaloids (from *Cannabis sativa*) with well-described euphoric, sedating, analgesic, antiemetic, and appetite-stimulating properties. In 1990, several groups cloned brain cannabinoid receptors which bound with high affinity to delta<sup>9</sup>-tetrahydrocannabinol (THC), the principal psychoactive component of marijuana and related preparations. It was later shown that a condensation product of two constituents of lipid membranes, arachidonic acid and ethanolamine, known as anandamide (arachidonyl ethanolamine), was the endogenous ligand for the cannabinoid receptor [38]. There is evidence for two distinct subtypes of cannabinoid receptor, designated CB<sub>1</sub> and CB<sub>2</sub> [39]. CB receptors are G-protein-coupled receptors. The exact physiological functions of CB receptors are not known, though a recent study with CB<sub>1</sub> transgenic mice (with "knockout" of the CB<sub>1</sub> receptor) demonstrated an attenuated morphine withdrawal behavioral syndrome [40]. There is strong evidence that cannabi-

noid administration increases, and cannabinoid abstinence decreases, mesolimbic DA release [41], suggesting that mesolimbic DA systems subserve the reinforcing effects of cannabinoids.

#### F. Phencyclidine (PCP):

Also known as angel dust, PCP is an arylcyclohexylamine which has well-described psychotomimetic properties. In healthy human subjects, it produces a constellation of cognitive and clinical symptoms which resemble a schizophrenic psychosis [42], and produces cognitive deficits similar to those present in schizophrenic patients when repeatedly administered to nonhuman primates and rats [24,43]. PCP binds to the NMDA receptor complex at its noncompetitive (ion channel) site. It closely resembles the actions of ketamine, a dissociative anesthetic and veterinary tranquilizer, which produces similar effects in human subjects. At higher concentration, PCP is known to inhibit the DAT, which could contribute to its propensity to lead to positive symptoms of psychosis such as delusions, hallucinations and thought disorder. It is chemically similar to ketamine ("Special K"), a frequently abused psychotogenic and recreational drug.

#### G. Methylendioxyamphetamine (MDMA; Ecstasy)

MDMA is a psychedelic drug which is a derivative of methamphetamine that has become frequently abused by young adults, particularly at "rave" parties [44]. Typical single doses of MDMA are 100–200 mg, and it produces a "rush" similar to methamphetamine lasting 3–4 hours and feelings of "connectedness," tranquility, apathy, and alterations in time perception. While not well studied, there may be a withdrawal syndrome associated with MDMA cessation in chronic users which resembles psychostimulant abstinence. Its mechanism involves indirect 5HT agonist activity by potentiation of 5HT release and through 5HT reuptake blockade. Further, there is evidence that it inhibits the synthesis of 5HT and that it may be toxic to serotonergic neurons. It has been associated with a post-hallucinogen perception disorder reminiscent of that observed with LSD, and with serotonin syndrome, because of excessive central serotonergic activity. At present, no specific pharmacologic treatment exists for MDMA abuse.

## VI. CLINICAL ASSESSMENT OF THE DRUG-ADDICTED INDIVIDUAL: IMPLICATIONS FOR PHARMACOTHERAPY OF ADDICTIVE DISORDERS

The emerging biological knowledge about drug addictions has had profound implications for our treatment approaches to addictive disorders. In this section, I will briefly discuss available pharmacotherapies for addictive disorders, including opioid, nicotine, and cocaine (stimulant) addiction. Subsequently, I will describe a general approach to the assessment and treatment of individuals with addictive disorders in three specific populations: the monodrug user; the polydrug user; and the drug user with a comorbid psychiatric disorder(s).

### A. Specific Pharmacotherapies for Addictive Disorders

#### 1. Pharmacotherapy of Opioid Dependence

##### *Methadone (Including LAAM).*

This full  $\mu$ -opioid receptor agonist has become the mainstay of opioid maintenance treatment in the United States [45]. The pioneering studies of Dole and Nyswander established its efficacy as a treatment for opioid addiction in the 1960s [16]. The drug is classified as a schedule II controlled substance by the Drug Enforcement Agency (DEA), and can only be administered in federally sponsored methadone programs which require careful monitoring of patients and weekly drug counseling [46]. The half-life of the drug is 24–36 hr in patients without hepatic disease, and methadone is primarily metabolized by the CYP 3A4 system. Patients beginning treatment are generally started on a daily dose of 20–30 mg/day, with weekly dose increases of 5–10 mg/day until a dose of 60–100 mg/day is achieved, that produces full suppression of opioid craving symptoms and resultant opioid-free urine toxicology [46]. Patients generally stay on methadone for 6 months to 3 years, although it is still common for some patients to receive lifelong methadone maintenance. A longer-acting derivative of methadone (L-alpha-acetomethadol; LAAM) is also FDA approved, and because of its long half-life (48–72 hr) can be given three times per week.

##### *Naltrexone (Trexan)*

Naltrexone is a long-acting (half-life ~ 24 hr) congener of naloxone, the short-acting (half-life ~ 0.5 hr)  $\mu$ -opioid receptor antagonist. It is generally given to opioid-dependent individuals who have been successfully detoxified from opioids; in opioid-dependent patients, administration will produce the rapid onset of the opioid withdrawal syndrome. It is typically started at 12.5–25 mg/day once daily with food, and titrated to a dose of 50–100 mg/day. Nausea and gastric irritation are common side effects. Liver function tests should be obtained at baseline prior to initiation of treatment since naltrexone is associated with elevation of transaminases and, rarely hepatotoxicity, necessitating periodic monitoring of liver function [47]. In addition, naltrexone (ReVia) was approved in 1992 for the treatment of alcohol dependence [13,14].

##### *Buprenorphine (Subutex)*

Buprenorphine is a partial  $\mu$ -opioid receptor agonist and  $\kappa$ -antagonist which is expected to be approved for the treatment of opioid dependence in 2001. Several recent clinical trials have established its safety and efficacy (comparable to methadone) in opioid-dependent patients [48,49]. Because of its partial agonist properties, it appears to be safer in drug overdoses, and since it has a half-life of 36 hr, it can be given three times per week. Because of its safety and convenience of dosing, it may be useful for the treatment of opioid addiction in primary care settings, which is especially helpful since most opioid addicts have significant medical problems (e.g., hepatitis B/C, HIV). Buprenorphine will be available in 4- and 8-mg tablets, and as a combination tablet with naloxone (Suboxone; to reduce illegal diversion of the medication) it is also likely to be approved by the FDA by the end of 2001. The daily maintenance dose of buprenorphine is 24–36 mg/day.

#### 2. Pharmacotherapy of Nicotine Dependence

##### *Nicotine Replacement Therapies (NRTs)*

The best studied of the pharmacological treatments for tobacco addiction are the nicotine replacement therapies (NRTs), which include the nicotine gum, nicotine patch, nicotine nasal spray, and nicotine inhaler [33,50,51]. The more slowly absorbed formu-

lations (gum and patch) appear to be helpful to alleviate nicotine withdrawal symptoms, and the faster-absorbed preparations (nasal spray and inhaler) appear to better substitute for the rewarding effects of cigarettes. The smoking cessation rates at the end of treatment are typically 50–70%, and 30–40% of subjects remained abstinent at 6- and 12-month follow-up assessments [52]. The gum and patch are available over the counter (OTC), but the nasal spray and inhaler are prescription drugs. Unfortunately, the cost of these preparations (\$25–35/week) are prohibitive for many smokers who want to quit, and the prescription preparations are often not covered by health insurance [52].

#### *Sustained-Release Bupropion*

Bupropion is a heterocyclic antidepressant agent which was approved by the FDA for the treatment of depression (Wellbutrin) in the late 1980s. Several clinical studies in the early 1990s documented that it could reduce smoking [53–55], and the drug was approved as a treatment for nicotine dependence by the FDA in 1997 as Zyban. The initial dose is 150 mg PO QD, and the dose is increased to 150 mg PO BID (300 mg/day) by the second week of treatment; patients are encouraged to try to quit smoking when they reach the 300 mg/day dose. Treatment with Zyban is recommended for 6–12 weeks. Smoking cessation rates with Zyban are typically higher than for the nicotine patch, but are reduced after the medication is discontinued [54], and there appears to be a modest (but nonsignificant) improvement in quit rates when Zyban is combined with the nicotine patch [56]. A history of seizures is a contraindication for the use of this drug.

#### *Other Promising Agents for the Treatment of Nicotine Addiction*

Other, nonapproved agents which may be useful for the treatment of nicotine addiction include clonidine [57,58]; an  $\alpha_2$  agonist which may reduce withdrawal symptoms; buspirone [59], a 5HT<sub>1a</sub> agonist and anxiolytic agent; nortriptyline [60], a tricyclic antidepressant; moclobemide [61], a monoamine oxidase A inhibitor; and the combination of nicotine patch and mecamylamine, a high-affinity nicotinic receptor antagonist [62,63].

### 3. *Pharmacotherapy of Cocaine (Stimulant)* *Dependence*

#### *Desipramine and Other Tricyclic Antidepressants (TCAs)*

Desipramine hydrochloride (DMI) is the best-studied TCA, and several early studies (particularly those which used open-label designs [64]), and three placebo-controlled studies at Yale [65,66], found that DMI was efficacious for reducing cocaine use in cocaine-dependent subjects. However, the results of subsequent placebo-controlled studies, including those at other sites, have been equivocal, and based on a meta-analysis of the initial six placebo-controlled trials, the efficacy of DMI for cocaine addiction treatment has been questioned [67]. Similar equivocal findings have been reported with imipramine [68] for both cocaine and methamphetamine addiction. However, DMI and other TCAs may have some benefit in cocaine-addicted individuals with a history of depression [69].

#### *Selective Serotonin Reuptake Inhibitors (SSRIs)*

There is little evidence that SSRI drugs are effective treatments for cocaine dependence [70], except perhaps in individuals with comorbid major depressive symptoms.

#### *Dopaminergic Agonists and Antagonists*

Amantadine and bromocriptine have shown limited success [71,72], but dopamine D<sub>2</sub> antagonists (chlorpromazine, haloperidol) have not [73]. D<sub>1</sub> agonists have looked promising in animal self-administration studies [32] and in human cue reactivity studies [74], but preliminary clinical trials have not been encouraging. Bupropion, a catecholamine reuptake inhibitor, and mazindol, a selective dopamine reuptake inhibitor, have also not shown efficacy in cocaine pharmacotherapy trials [75,76].

#### *Disulfiram*

Disulfiram, best known as an aldehyde dehydrogenase inhibitor used in the treatment of alcohol dependence, has been shown in three studies at Yale University to have efficacy for the treatment of cocaine addiction [65,66,77]. Its mechanism of action appears to be independent of effects in reducing comorbid alco-

hol use [66], and it may act through increasing plasma cocaine levels by inhibiting plasma esterases which metabolize [78], and inhibition of the dopamine- $\beta$ -hydroxylase (DBH), the enzyme that converts dopamine to norepinephrine, thus presumably increasing synaptic DA levels, which are thought to be depleted in chronic cocaine users. The drug is associated with some toxicity (e.g., transaminase elevations, psychotic reaction) and with severe reactions when combined with alcohol, so widespread use for the treatment of cocaine addiction may be limited.

## B. Approach to the Addicted Individual

### 1. *The Monodrug User*

The approach to the monodrug using patients entails selecting an effective agent for the treatment of the single addictive disorder. Such effective treatments are available for opioid dependence (e.g., methadone, buprenorphine), alcohol dependence (e.g., disulfiram and naltrexone), and tobacco (nicotine replacement therapies, sustained-release bupropion), but not as yet for cocaine or other psychostimulants. The effectiveness of these pharmacotherapies has been reviewed elsewhere, and is greatly enhanced by the patient's motivation to quit using drugs at the beginning of treatment [79,80], though effective addiction pharmacotherapies can often be helpful in those individuals without substantial motivation to quit (e.g., the individual who just wants to take a pill, rather than do behavioral treatment). With respect to pharmacotherapies, one must strive to use the safest agent available (minimal side effects) balanced with one that will have treatment effectiveness. Accordingly, in an opioid-dependent patient who is noncompliant with treatment and at risk for drug overdose, treatment with buprenorphine (which can be given three times daily and has minimal overdose potential) might be preferable to methadone (daily administration, high risk of overdose) treatment. Use of structured assessment scales like the Addiction Severity Index (ASI [81]) provides multimodal assessment of preexisting functional impairment prior to drug treatment, and can provide individualized information that can be used to tailor treatments (e.g., treatment matching).

### 2. *The Polydrug User*

Similarly, any effective pharmacotherapy(ies) for the individual drug abused may be helpful, but targeting only one drug of abuse in a polysubstance abuser is often likely to fail since the use of one drug of abuse

can condition use of another (e.g., a cocaine user who also injects heroin and drinks alcohol during cocaine binges may promote cocaine craving after initial abstinence if he uses heroin or alcohol). Furthermore, the severity of addiction is likely to be higher in the polydrug abuser and these patients are more likely to have concurrent (chronic) mental and medical illness [82] and therefore to have poor treatment outcomes. In general, if one of the drugs of abuse has a defined pharmacotherapy (e.g., heroin), then a specific treatment can be initiated (e.g., methadone, naltrexone) and this addiction stabilized, prior to addressing abuse of a substance that does not have a well-established pharmacotherapy (e.g., concurrent cocaine dependence in a methadone-maintained individual).

### 3. *The Drug User with Psychiatric Comorbidity*

The psychiatric drug abuser poses considerable diagnostic and therapeutic challenges for clinicians, and the therapeutic approach taken with these "dually diagnosed" individuals is often colored by the treatment philosophy of the treating clinician (e.g., mental health versus addictions treatment provider). Accordingly, mental health clinicians tend to underemphasize (or ignore) substance abuse treatment in their psychiatric patients, and primary substance abuse providers tend to overlook psychiatric issues in their patients [83]. Given the typical fragmentation of mental health and addictions treatment in most health care systems, these individuals often "fall between the cracks," and in many cases this is related to their low motivation to receive treatment [84], which is frequently related to a lack of insight into the severity of their combined mental health and addiction problems. Nonetheless, in cases where individuals may be self-medicating psychiatric symptoms with substances of abuse (e.g., the depressed cocaine user), pharmacotherapies directed at the underlying psychiatric disorder may be useful. For example, it has been shown that the tricyclic antidepressant desipramine, which may have some efficacy in the pharmacotherapy of cocaine dependence, may be especially effective in depressed cocaine addicts [69]. Furthermore, individuals with schizophrenia may use nicotine to alleviate clinical (e.g., negative symptoms, extrapyramidal side effects) and cognitive (e.g., working memory, attentional) deficits associated with this illness [53,85]. There is evidence that the atypical antipsychotic drug clozapine [86–88] can reduce smoking and that clozapine and other atypical antipsychotic drugs such as risperidone and olanzapine can increase smoking cessation rates in combination with the nico-

tine transdermal patch, compared to typical antipsychotic agents (e.g., haloperidol, chlorpromazine) [89]. Methods that increase compliance with pharmacotherapies, like using medications with minimal side effects (e.g., SSRIs vs. TCAs in substance-abusing depressed patients; atypical antipsychotic drugs in drug-abusing schizophrenics), medications that can be given once daily, or by injection on a monthly or bimonthly basis (e.g., haloperidol and fluphenazine decanoate, respectively), and those with low overdose potential (e.g., anticonvulsant mood stabilizer [e.g., sodium valproate or gabapentin] vs. lithium in a substance abuser with bipolar disorder) are all strategies to deliver more effective and tolerable treatment in dually diagnosed individuals. More research is needed on the efficacy of substance abuse pharmacotherapies in psychiatric populations, but conducting such research is difficult owing to the poor compliance of dually diagnosed subjects with the study interventions, and the high subject attrition rates in these trials. Nonetheless, conducting research in dually diagnosed subjects will yield important new information which can guide clinicians as to what pharmacological and behavioral interventions are useful and practical in this challenging patient population.

#### **VII. TREATMENT OPTIMIZATION: COMBINATION OF BIOLOGICAL AND PSYCHOSOCIAL (BEHAVIORAL) TREATMENT OF ADDICTIVE DISORDERS**

Use of substance abuse pharmacotherapies is most effective when combined with standardized psychosocial (behavioral) treatments for these disorders [90]. For individuals who are attempting abstinence initiation (e.g., trying to stop using drugs), the motivational enhancement therapies, which encourage individuals to make the choice to become abstinent for their own reasons, are the psychosocial therapy of choice. Individuals who have stopped using drugs and who want to maintain their sobriety from drug use are best treated with the relapse prevention therapies, a derivative of cognitive-behavioral therapies, which emphasize strategies for avoiding cues that promote drug relapse (people, places, and things associated previously with their drug use). Several studies have reported an interaction between pharmacotherapeutic and psychotherapeutic interventions [60,90]. In fact, in federally funded methadone maintenance programs,

drug counseling is a mandatory part of treatment with methadone [46].

#### **VIII. CONCLUSIONS**

There is increasing preclinical and clinical evidence for a biological basis to addictive disorders, which should lead to a new era of innovative and effective pharmacotherapies for addictive disorders. Addictive disorders should be considered as chronic medical disorders like hypertension, schizophrenia, and diabetes [1], given the long-term nature of these disorders, frequent symptom relapse, need for extended treatment, and absence of any "cure" for these disorders. The common biological system that appears to be involved in the pathophysiology of all addictive disorders is the mesolimbic dopamine (DA) system, but other neural pathways including the endogenous opioid peptide systems and the HPA axis are probably of relevance to several addictive drugs, including opioids, alcohol, cocaine, and nicotine. Treatments for these addictive disorders are increasing with the emerging knowledge of the biological basis of addiction, but one glaring deficit is the absence of an effective pharmacotherapy for cocaine dependence and other illicit psychostimulant addictions. The effective use of any such pharmacotherapy for addictive disorders will necessitate combination with effective psychosocial treatments for addiction, especially given the complex biological, psychological, and social aspects of addictive illnesses.

#### **ACKNOWLEDGMENTS**

Supported in part by grants P50-DA-12762 (PI: T.R. Kosten), P50-DA-13334 (PI: S.S. O'Malley) and R01-DA-14039 (to T.P.G.) from the National Institute on Drug Abuse (NIDA), the VISN 1 Mental Illness Research, Education and Clinical Center (MIRECC) of the Department of Veterans Affairs and a Wodecroft Foundation Young Investigator Award from the National Alliance for Research on Schizophrenia and Depression (NARSAD) to T.P.G. The helpful comments of Thomas R. Kosten, M.D. and Richard S. Schottenfeld, M.D. on the manuscript are gratefully acknowledged.

#### **REFERENCES**

1. McLellan AT, Lewis DC, O'Brien CP, Kleber HD. Drug dependence, a chronic medical illness.

- Implications for treatment, insurance and outcomes evaluation. *JAMA* 2000;284:1689-1695.
2. O'Brien CP. A range of research-based pharmacotherapies for addiction. *Science* 1997;287:66-70.
  3. Frances A, Pincus HA, First MB. Diagnostic and Statistical Manual of Mental Disorders, 4th ed (DSM-IV). Washington; American Psychiatric Association, 1994:886.
  4. Wise RA. Drug-activation of brain reward pathways. *Drug Alcohol Depend* 1998;51:13-22.
  5. Spanagel R, Weiss F. The dopamine hypothesis of reward: past and current status. *Trends Neurosci* 1999;22:521-527.
  6. Horvitz JC. Mesolimbocortical and nigrostriatal dopamine responses to salient non-reward events. *Neuroscience* 2000;96:651-656.
  7. Koob GF, Le Moal M. Drug addiction, dysregulation of reward, and allostasis. *Neuropsychopharmacology* 2001;24:97-129.
  8. Spanagel R. Modulation of drug-induced sensitization process by endogenous opioid systems. *Behav Brain Res* 1995;70:37-49.
  9. Sesack SR, Pickel VM. Dual ultrastructural localization of enkephalin and tyrosine hydroxylase immunoreactivity in the rat ventral tegmental area: multiple substrates for opiate-dopamine interactions. *J Neurosci* 1992;12:1335-1350.
  10. Shieh K-R, Pan J-T. Nicotinic control of tuberoinfundibular dopaminergic neuron activity and prolactin secretion: diurnal rhythm and involvement of endogenous opiate system. *Brain Res* 1997;756:266-272.
  11. George TP, Verrico CD, Xu L, Roth, RH. Effects of repeated nicotine administration and footshock stress on rat mesoprefrontal dopamine systems: evidence for opioid mechanisms. *Neuropsychopharmacology* 2000;23(1):79-88.
  12. Krishnan-Sarin S, Rosen MI, O'Malley SS. Evidence for an opioid component in nicotine dependence. *Arch. Gen. Psychiatry* 1999;56:663-668.
  13. O'Malley SS, Jaffe AJ, Chang G, Schottenfeld RS, Meyer RE, Rounsaville B. Naltrexone and coping skills therapy for alcohol dependence: a controlled study. *Arch. Gen. Psychiatry* 1992;49:881-887.
  14. Volpicelli JR, Alterman AI, Hayashida M, O'Brien CP. Naltrexone in the treatment of alcohol dependence. *Arch Gen Psychiatry* 1992;49:876-880.
  15. Spangler R, Zhou Y, Schussman SD, Ho A, Kreek MJ. Prodynorphin, proenkephalin and kappa opioid receptor mRNA responses to acute "binge" cocaine. *Mol Brain Res* 1997;44:139-142.
  16. Kreek MJ, Koob GF. Drug dependence: stress and dysregulation of brain reward pathways. *Drug Alcohol Depend* 1998;51:23-47.
  17. Masukawa Y, Suzuki T, Misawa M. Differential modification of the rewarding effects of methamphetamine and cocaine by opioids and antihistamines. *Psychopharmacology* 1993;111:139-143.
  18. Shaham Y, Erb S, Stewart J. Stress-induced relapse to heroin and cocaine seeking in rats: a review. *Brain Res Rev* 2000;33:13-33.
  19. Cone EJ, Kumor K, Thompson LK, Sherer M. Correlation of saliva cocaine levels with plasma levels and with pharmacologic effects after intravenous cocaine administration in human subjects. *J Anal Toxicol* 1988;12:200-206.
  20. Ma F, Falk JL, Lau CE. Cocaine pharmacodynamics after intravenous and oral administration in rats: relation to pharmacokinetics. *Psychopharmacology* 1999;144:323-332.
  21. Koob GF, Le Moal M. Drug abuse: hedonic homeostasis dysregulation. *Science* 1997;278:52-58.
  22. Robinson TE, Berridge KC. The psychology and neurobiology of addiction: an incentive-sensitization view. *Addiction* 2000;95(suppl 2):S91-S117.
  23. Grace AA. The tonic/phasic model of dopamine system regulation and its implications for understanding alcohol and stimulant craving. *Addiction* 2000;95(suppl 2):S119-S128.
  24. Jentsch JD, Taylor JR. Impulsivity resulting from frontostriatal dysfunction in drug abuse: implications for the control of behavior by reward-related stimuli. *Psychopharmacology* 1999;146:373-390.
  25. Breiter HC, Gollub RL, Weisskoff RM, et al. Acute effects of cocaine on human brain activity and emotion. *Neuron* 1997;19:591-611.
  26. Grace AA. Cortical regulation of subcortical dopamine systems and its possible relevance to schizophrenia. *J Neural Transm* 1993;91:111-134.
  27. Bolla KI, Funderburk FR, Cadet JL. Differential effects of cocaine and cocaine alcohol on neurocognitive performance. *Neurology* 2000;54:2285-2292.
  28. Kosten TR. Pharmacotherapy of cerebral ischemia in cocaine dependence. *Drug Alcohol Depend* 1998;49:133-144.
  29. Mendelson JH, Mello NK. Management of cocaine abuse and dependence. *N Engl J Med* 1996;334:965-972.
  30. Horger BA, Iyasere CA, Berhow MT, Messer CJ, Nestler EJ, Taylor JR. Enhancement of locomotor activity and conditioned reward to cocaine by brain-derived neurotrophic factor. *J Neurosci* 1999;19:4110-4122.
  31. Nestler EJ. Genes and addiction. *Nat Genet* 2000;26:277-281.
  32. Self DW, Nestler EJ. Relapse to drug-seeking: neural and molecular mechanisms. *Drug Alcohol Depend* 1998;51:49-60.
  33. Balfour DJK, Fagerstrom KO. Pharmacology of nicotine and its therapeutic use in smoking cessation and neurodegenerative disorders. *Pharmacol Ther* 1996;72:51-81.

34. Picciotto MR, Caldarone BJ, King SL, Zachariou V. Nicotinic receptors in the brain: links between molecular biology and behavior. *Neuropsychopharmacology* 2000;22:451-465.
35. Clarke PBS, Fu DS, Jakubovic A, Fibiger HC. Evidence that mesolimbic dopamine activation underlies the locomotor stimulant action on nicotine in rats. *J Pharmacol Exp Ther* 1988;246:701-708.
36. Fowler JS, Volkow ND, Wang G-J, et al. Inhibition of monoamine oxidase B in the brains of smokers. *Nature* 1996;379:733-736.
37. Fowler JS, Volkow ND, Wang G-J, et al. Brain monoamine oxidase A: inhibition by cigarette smoke. *Proc Natl Acad Sci USA* 1996;93:14065-14069.
38. Devane WA, Hanus L, Breuer A, et al. Isolation and structure of a brain constituent that binds to the cannabinoid receptor. *Science* 1992;258:1882-1884.
39. Pertwee R. Pharmacology of cannabinoid receptor ligands. *Curr Med Chem* 1999;6:635-664.
40. Ledent C, Valverde O, Cossu G. Unresponsiveness to cannabinoids and reduced addictive effects of opiates in CB1 receptor knockout mice. *Science* 1999;283:401-404.
41. Tanda G, Loddo P, Di Chiara G. Dependence of mesolimbic dopamine transmission on delta9-tetrahydrocannabinol. *Eur J Pharmacol* 1999;376:23-26.
42. Krystal JH, Karper LP, Seibyl JP, et al. Subanesthetic effects of the non-competitive NMDA antagonist, ketamine in humans: psychotomimetic, perceptual, cognitive and neuroendocrine responses. *Arch Gen Psychiatry* 1994;51:199-214.
43. Jentsch JD, Redmond DE Jr, Elsworth JD, Taylor JR, Youngren KD, Roth RH. Enduring cognitive deficits and cortical dopamine dysfunction in monkeys after long-term administration of phencyclidine. *Science* 1997;277:953-955.
44. McCann UD, Eligulashvili V, Ricaurte GA. (+/-)-3,4-Methylenedioxyamphetamine ("Ecstasy")-induced serotonin neurotoxicity: clinical studies. *Neuropsychobiology* 2000;42:11-16.
45. O'Connor PG, Fiellin DA. Pharmacologic treatment of heroin-dependent patients. *Ann Intern Med* 2000;133:40-54.
46. Judd LL, Attkisson C, Berrettini W, et al. Effective medical treatment of opiate addiction. *JAMA* 1998;280:1936-1943.
47. Verebey KG, Mule SJ. Naltrexone (Trexan): a review of hepatotoxicity issues. *NIDA Res Monogr* 1986;67:73-81.
48. Ling W, Charuvastra C, Collins JF, et al. Buprenorphine maintenance treatment of opiate dependence: a multicenter, randomized clinical trial. *Addiction* 1998;93:475-486.
49. Schottenfeld RS, Pakes JR, Oliveto A, Zeidonis D, Kosten TR. Buprenorphine versus methadone maintenance treatment for concurrent opioid dependence and cocaine abuse. *Arch Gen Psychiatry* 1997;54:713-720.
50. Hughes JR. The future of smoking cessation therapy in the United States. *Addiction* 1996;91(12):1797-1802.
51. Ziedonis DM, Wyatt SA, George TP. Current issues in nicotine dependence and treatment. In: *New Treatments in Chemical Addictions*, eds TR Kosten, EF McCance-Katz. Washington: American Psychiatric Press, 1998;1-34.
52. Hughes JR, Goldstein MG, Hurt RD, Shiffman S. Recent advances in the pharmacotherapy of smoking. *JAMA* 1999;281:72-76.
53. Ziedonis DM, George TP. Schizophrenia and nicotine use: report of a pilot smoking cessation program and review of neurobiological and clinical issues. *Schizophr Bull* 1997;23(2):247-254.
54. Hurt RD, Sachs DPL, Glover ED, et al. A comparison of sustained-release bupropion and placebo for smoking cessation. *N Engl J Med* 1997;337:1195-1202.
55. Ferry LH, Burchette RJ. Efficacy of bupropion for smoking cessation in non-depressed smokers. *J Addict Dis* 1994;13:249.
56. Jorenby DE, Leischow SJ, Nides MA, et al. A controlled trial of sustained-release bupropion, a nicotine patch, or both for smoking cessation. *N Engl J Med* 1999;340:685-691.
57. Glassman AH, Stetner F, Walsh BT, et al. Heavy smokers, smoking cessation, and clonidine. *JAMA* 1988;259:2863-2866.
58. Glassman AH, Covey LS, Dalack GW, et al. Smoking cessation, clonidine, and vulnerability to nicotine among dependent smokers. *Clin Pharmacol Ther* 1993;54(6):670-679.
59. Cinciripini PM. A placebo-controlled evaluation of the effects of buspirone on smoking cessation: differences between high- and low-anxiety smokers. *J Clin Psychopharmacol* 1995;15:182-191.
60. Hall SM, Reus VI, Munoz RF, et al. Nortriptyline and cognitive-behavioral therapy in the treatment of cigarette smoking. *Arch Gen Psychiatry* 1998;55:683-690.
61. Berlin I, Said S, Spreux-Varoquaux O, et al. A reversible monoamine oxidase A inhibitor (moclobemide) facilitates smoking cessation and abstinence in heavy, dependent smokers. *Clin Pharmacol Ther* 1995;58:444-452.
62. Rose JE, Behm FM, Westman EC, Levin ED, Stein RM, Ripka GV. Mecamylamine combined with nicotine skin patch facilitates smoking cessation beyond nicotine patch treatment alone. *Clin Pharmacol Ther* 1994;56(1):86-99.
63. Rose JE, Behm FM, Westman EC. Nicotine-mecamylamine treatment for smoking cessation: the role of

- pre-cessation therapy. *Exp Clin Psychopharmacol* 1998;6(3):331-343.
64. Gawin FH, Kleber HD. Cocaine abuse treatment: Open pilot trial with desipramine and lithium carbonate. *Arch Gen Psychiatry* 1984;41:903-910.
  65. Carroll KM, Nich C, Ball SA, McCance E, Rounsaville BJ. Treatment of cocaine and alcohol dependence with psychotherapy and disulfiram. *Addiction* 1998;93:713-728.
  66. George TP, Chawarski MC, Pakes J, Carroll KM, Kosten TR, Schottenfeld RS. Disulfiram versus placebo for cocaine dependence in buprenorphine-maintained subjects: a preliminary study. *Biol Psychiatry* 2000;47:1080-1086.
  67. Levin FR, Lehman AF. Meta-analysis of desipramine as an adjunct in the treatment of cocaine addiction. *J Clin Psychopharmacol* 1991;11:374-383.
  68. Galloway GP, Newmeyer J, Knapp T, et al. Imipramine for the treatment of cocaine and methamphetamine dependence. *J Addict Dis* 1994;13:201-208.
  69. Ziedonis DM, Kosten TR. Depression as a prognostic factor for pharmacological treatment of cocaine dependence. *Psychopharmacol Bull* 1991;27:337-343.
  70. Grabowski J, Rhoades H, Elk R, et al. Fluoxetine is ineffective for treatment of cocaine dependence or concurrent opioid and cocaine dependence. Two placebo-controlled, double-blind trials. *J Clin Psychopharmacol* 1995;15:163-178.
  71. Gawin FR, Morgan C, Kosten TR, et al. Double-blind evaluation of the effect of acute amantadine on cocaine craving. *Psychopharmacology* 1989;97:402-407.
  72. Kosten TR, Morgan CM, Falcione J, Schottenfeld RS. Pharmacotherapy for cocaine-abusing methadone-maintained patients using amantadine or desipramine. *Arch Gen Psychiatry* 1992;49:894-898.
  73. Warner EA, Kosten TR, O'Connor PG. Pharmacotherapy for opioid and cocaine abuse. *Med Clin North Am* 1997;81:909-925.
  74. Haney M, Collins ED, Ward AS, Foltin RW, Fischman MW. Effect of a selective dopamine D1 agonist (ABT-431) on smoked cocaine self-administration in humans. *Psychopharmacology* 1999;143:102-110.
  75. Stine SM, Krystal JH, Kosten TR, Charney DS. Mazindol treatment of cocaine dependence. *Drug Alcohol Depend* 1995;39:245-252.
  76. Margolin A, Kosten TR, Avants SK, et al. A multicenter trial of bupropion for cocaine dependence in methadone-maintained patients. *Drug Alcohol Depend* 1995;40:125-131.
  77. Petrakis IL, Carroll KM, Nich C, et al. Disulfiram treatment for cocaine dependence in methadone-maintained opioid addicts. *Addiction* 2000;95:219-228.
  78. McCance-Katz EF, Kosten TR, Jatlow PI. Disulfiram effects on acute cocaine administration. *Drug Alcohol Depend* 1998;57:27-39.
  79. Miller WR, Rollnick S. *Motivational Interviewing*. New York: Guilford Press, 1991.
  80. Prochaska JO, DiClemente CC. Stages and processes of self-change of smoking: Toward an integrative model of change. *J Consult Clin Psychol* 1983;51(3):390-395.
  81. McLellan AT, Kuschner T, Metzger H, et al. The fifth edition of the addiction severity index. *J Subst Abuse Treatment* 1992;8:199-213.
  82. George TP, Krystal JH. Comorbidity of psychiatric and substance abuse disorders. *Curr Opin Psychiatry* 2000;13:327-331.
  83. Drake RE, Mercer-McFadden C, Mueser KT, McHugo GJ, Bond GR. Review of integrated mental health and substance abuse treatment for patients with dual disorders. *Schizophr Bull* 1998;24:589-608.
  84. Ziedonis DM, Trudeau K. Motivation to quit using substances among individuals with schizophrenia: implications for a motivation-based treatment model. *Schizophr Bull* 1997;23(2):229-238.
  85. Dalack GW, Healy DJ, Meador-Woodruff JH. Nicotine dependence and schizophrenia: clinical phenomenon and laboratory findings. *Am J Psychiatry* 1998;155:1490-1501.
  86. George TP, Sernyak MJ, Ziedonis DM, Woods SW. Effects of clozapine on smoking in chronic schizophrenic outpatients. *J Clin Psychiatry* 1995;56(8):344-346.
  87. McEvoy JP, Freudenreich O, Wilson WH. Smoking and therapeutic response to clozapine in patients with schizophrenia. *Biol Psychiatry* 1999;46:125-129.
  88. McEvoy J, Freudenreich O, McGee M, VanderZwaag C, Levin E, Rose J. Clozapine decreases smoking in patients with chronic schizophrenia. *Biol Psychiatry* 1995;37:550-552.
  89. George TP, Ziedonis DM, Feingold A, et al. Nicotine transdermal patch and atypical antipsychotic medications for smoking cessation in schizophrenia. *Am J Psychiatry* 2000;157(11):1835-1842.
  90. Carroll KM. Manual-guided psychosocial treatment: a new virtual requirement for pharmacotherapy trials? *Arch Gen Psychiatry* 1997;54:923-928.