Cocaine Use in Pregnancy

Women addicted to cocaine often continue drug use through pregnancy, despite risks to the fetuses they are carrying. Primate studies have shown that intrauterine cocaine exposure (during a period corresponding to the second trimester in humans) results in a decrease in the number of neurons in the cerebral cortex and disorganization of the normal laminar structure of the cortex [56, 57]. Even brief exposure at a particularly vulnerable time in brain development may have lasting deleterious effects of greater magnitude than greater exposures at other times [58]. Moreover, the postnatal age at which the effects of cocaine are measured, whether in humans or animals, may show evolving outcomes [59]. In humans, the attribution of outcomes to drug effect is complicated by the observation that the circumstances under which children have been raised subsequent to cocaine exposure affect their behavior [60].

Cocaine and Pregnancy

* Increased incidence of stillbirths
* Increased incidence of miscarriages
* Premature (often fatal) labor and delivery
* In males, cocaine attaches to the sperm causing damage to the cells of the fetus.

Effects of Cocaine on the Fetus

* Seizures or strokes
* Cerebral palsy
* Mental retardation
* Vision and hearing impairments
* Urinary tract abnormalities
* Autism and learning disabilities
* Babies exposed to cocaine experience painful and life threatening withdrawal, are irritable, have poor ability to regulate their own body temperature and blood sugar and are at increased risk of having seizures.

E. Freye, *Pharmacology and Abuse of Cocaine, Amphetamines, Ecstasy and Related Designer Drugs*,
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Treatment Options in Cocaine Abuse

Since the cocaine user is prone for a relapse the primary goal in therapy is the prevention of further use. Within this frame, treatments for drug abuse are continually improving. For instance, for twenty-five years methadone was the only treatment for opiate dependence. Although LAAM (α-levoacetylmethadol) was removed from the European market due to reports of severe cardiac-related adverse events, and in 2003 Roxane Laboratories Inc. discontinued the product ORLAAM™ in the US. Presently, buprenorphine (Subutex®) and naltrexone (Trexan®, Revia®) are being used as treatment options [60]. Similarly, disulfiram, naltrexone and/or amprosate are being prescribed for alcohol dependence [61]. However, the treatment of cocaine abuse poses a more difficult challenge for addiction pharmacotherapy. In future, potential treatments may be based on immunopharmacotherapeutic agents that can suppress the effect of cocaine on behavioral and locomotive actions. At the horizon a second-generation vaccine is emerging, which protects against the psychoactive effects of cocaine [62]. Similarly a catalytic monoclonal antibody (mAB) is under development to bind and degrade cocaine by hydrolysing the benzoate ester of cocaine [63].

The actual mechanism whereby cocaine produces euphoria is still unknown. Presently, Sigma 1 receptors are being discussed as they are unique endoplasmic reticulum proteins that bind certain steroids, neuroleptics and psychotropic drugs. Sigma 1 receptors form a trimeric complex with ankyrin B and IP2R type 3 in NG-108 cells, which regulate Ca^{2+}-signalling may represent an active site for the binding of cocaine and neurosteroids [64].

Basically, however, there is a sequence of different steps in the treatment, which can be outlined as follows

1. Detoxification
2. Structured cocaine-free environment
3. Hospitalization or out-patient therapy
4. Pharmacologic therapy

Note, that this is treatment of abuse, not necessarily of “addiction”. It is hoped that abusive behavior can be curtailed before it develops into a full blown behavioral pattern. The elements of a program will vary according to the philosophy of the treatment organization, but most of those listed here will likely be included.

Detoxification

All too often this word means *cure* for many illicit users. As discussed in the previous chapters, the mere removal of the substance from the user is not sufficient to extinguish craving. While detoxification is essential, it’s only a first step in a rather lengthy process of recovery.

Cocaine-Free Environment

There are many factors that predispose individuals to use, and environment is certainly high on the list. To expose the recovering abuser to the same conditions that got them into use in the first place is to lose from the very start. If others in the patient's working or living arrangements are users, it will be difficult to extinguish craving, as there will be easy access to the substance when "drug hunger" calls.

Hospitalization or Outpatient Therapy

Depending upon the various factors (economics, environmental, psychological, physical) that apply, a decision must be made about the need for more or less supervision during detoxification and recovery.

Pharmacological Therapy

With new research adding to our understanding of cocaine's mechanism of action, pharmacologic intervention may prove to be of immense benefit in restoring the chemical imbalances caused by cocaine abuse. Pharmacologic therapy in cocaine addiction, however should not be confused with other pharmacologic approaches to dealing with drug abuse, such as methadone in opioid "replacement" therapy, or Trexan® (i.e. naltrexone, an opioid antagonist) in the rehabilitation phase. The latter compounds are used in the treatment of opioid dependency, and are directed at maintaining the physical state of the opioid addict, or preventing re-addiction of those addicts. Drugs used in the treatment of cocaine dependency are directed towards normalizing the chemical imbalances caused by cocaine, and reducing the craving for that drug. According to an early neurological model of addiction, cocaine-seeking behavior results from a deficit or imbalance of neurochemicals (neurotransmitters and neuromodulators), particularly dopamine. With the primary underlying deficit being depression, probably caused by depletion of dopamine, the target of drug therapy is either to treat the depression directly, or to restore the activity of the depleted neurotransmitter dopamine, since this neurotransmitter serves as a target messenger in the limbic system of the brain, causing feelings of reward. Under the traditional, though limited, assumption that dopamine depletion is the key to cocaine addiction, pharmacotherapies were developed using three alternate modes of dopamine substitution or restoration:

1. Substances that mimic the natural action of dopamine at its receptor sites in the reward area, such as bromocriptine mesylate or similar agents.
2. Substances that release dopamine, such as amantadine hydrochloride.
3. Substances that are used to synthesize dopamine, e.g., precursors, such as levodopa and L-tyrosine.

Aside from pharmacological treatment, restoration of neurotransmitter deficits with nutritional supplements seems a rational approach. By increasing the synthesis of neurotransmitters that are in short supply, they facilitate the release of the stimulant neurotransmitter dopamine, prevent the breakdown of enkephalin, and allow natural processes to stimulate the reward sites, leading to feelings of well-being. One promising approach to restoration of the neurotransmitter deficit involves precursor amino acids, and their production requires certain vitamins and minerals. While amino acid supplements have a long and useful history in the treatment of substance abuse, the "reward cascade" suggests that a specific mixture of amino acids and vitamins would be even more beneficial. One question in the use of amino acid precursors is the ability of these compounds to reach the brain from the blood in sufficient amounts. Large neutral amino acids (LNAAs), such as tryptophan, tyrosine, and phenylalanine, are transported across the blood-brain-barrier (BBB) by a special carrier. The BBB normally serves to isolate, to a large degree, fluids of the brain from compounds dissolved in blood plasma. There are a number of circumstances that can alter the action or effect of the LNAA carrier or of the BBB. Diet, stress, and drugs are three such factors. LNAA transport to the brain is virtually in direct relation to the concentration in the blood. Carbohydrate and protein rich diets have very different effects on blood LNAA concentrations. A carbohydrate meal increases insulin secretion. Insulin moves certain LNAAs to muscle and changes the amount of other LNAAs bound to blood proteins. Thus, carbohydrates increase the amount of tryptophan, tyrosine, and phenylalanine that reach the brain. A protein rich meal has the opposite effect.

L-Tryptophan

This amino acid is a food supplement and freely available in health food stores. Being an essential amino acid it means that it cannot be synthesized by the organism and therefore must be part of its diet. It is a precursor of serotonin and melatonin (Fig. 47), and may aid in the replenishment of that neurotransmitter. Clinical research confirmed tryptophan's effectiveness as a sleep aid [65, 66] and for a growing variety of other conditions typically associated with low serotonin levels or activity in the brain such as seasonal affective disorder [67]. In particular, tryptophan has been showing considerable promise as an antidepressant alone and as an "augmenter" of antidepressant drugs [68], although the reliability of these clinical trials has been questioned [69].

Also, the metabolite of tryptophan, i.e. 5-hydroxytryptophan (5-HTP), readily crosses the blood-brain barrier where it is rapidly decarboxylated to serotonin (5-hydroxytryptamine or 5-HT) [70] thus being suggested as a treatment for depression [70]. However, serotonin has a relatively short half-life since it is rapidly metabolized by monoamine oxidase, and therefore is likely to have limited efficacy.

L-Tyrosine

Similar to the previous amino acid this also serves as a precursor of dopamine synthesis, which may aid in the replenishment of that neurotransmitter (Fig. 48).

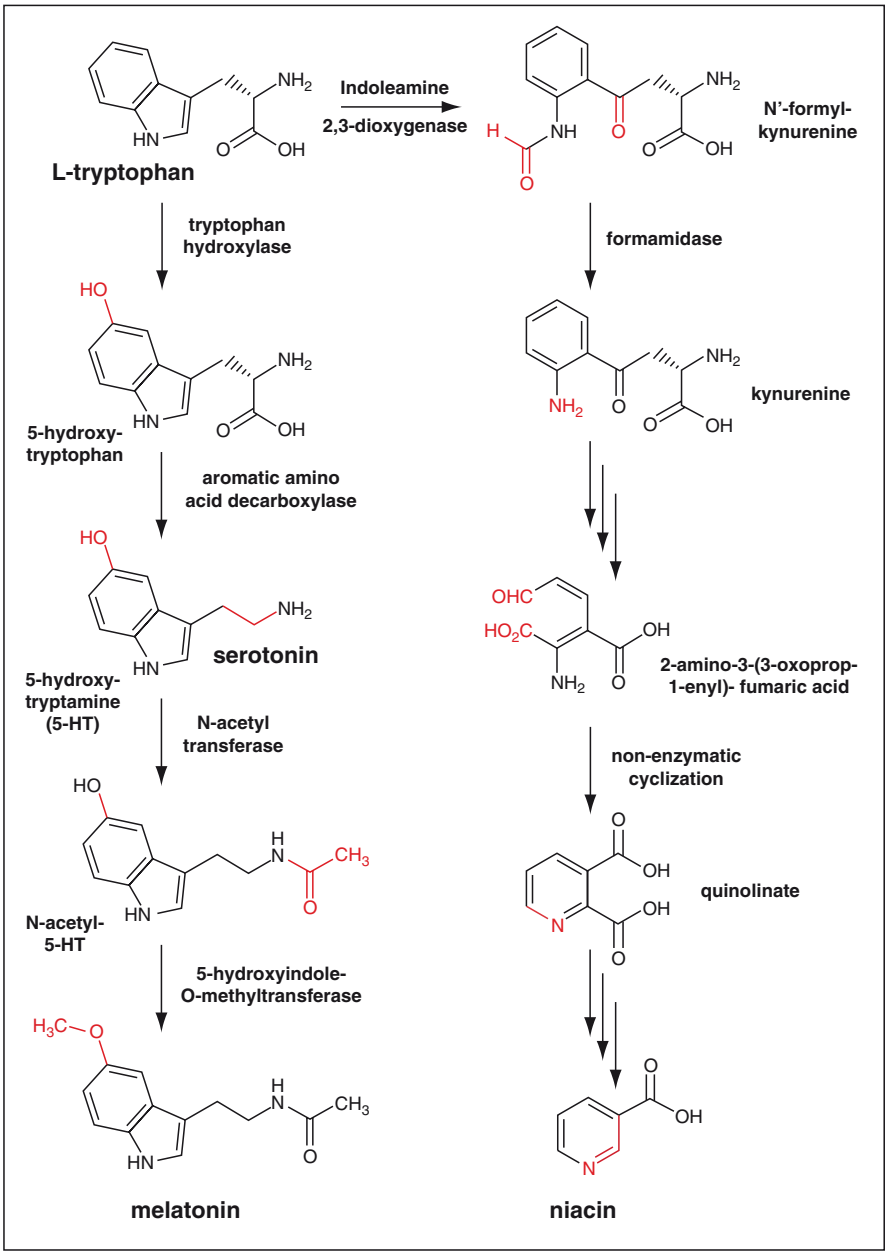

Fig. 47 Metabolism of L-tryptophan into serotonin, melatonin (*left*) and niacin (*right*). Transformed functional groups after each chemical reaction are highlighted in red.

In the adrenal gland, tyrosine is converted to levodopa by the enzyme tyrosine hydroxylase (TH). TH is also the rate-limiting enzyme involved in the synthesis of the catecholamine hormones dopamine, norepinephrine (noradrenaline), and

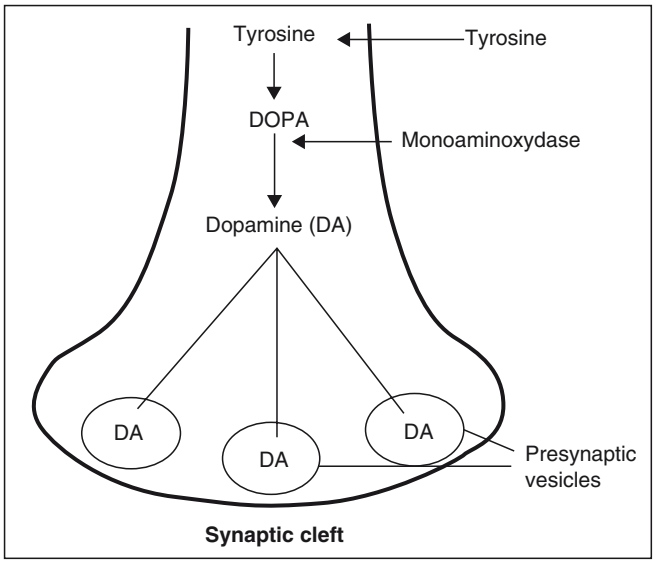

Fig. 48 Tyrosine being an essential amino acid in the synthesis of dopamine to relieve depression

epinephrine. Although tyrosine does not seem to have any significant effect on mood, cognitive or physical performance under normal circumstances, however, an effect on mood is more noticeable in humans subjected to stressful conditions [71–74]. The recommended daily dosage of 10 mg/kg for a body weight usually amounts to 500–1500 mg per day in the adult [71].

Use of Antidepressants to Relieve Post-cocaine Depression

The drugs of choice in the treatment of depression, the tricyclics, alter serotonin activity, an important neurotransmitter affected by cocaine, and relieve distressful symptoms. However, they are potentially cardiotoxic on their own, and have some other bothersome side effects such as heart rhythm disturbances, hypotonia, impaired liver function, weight gain, and/or bone marrow depression. These series of antidepressants are primarily designed to restore the balance of dopamine to functional levels. Under the assumption that depression is a contributory problem in cocaine addiction, monoamine oxidase inhibitors (e.g. phenelzine) or tricyclic anti-depressants (e.g. imipramine or desipramine) are used. These drugs not only interfere with the breakdown of dopamine, but reduce the breakdown of norepinephrine, a transmitter involved in depression.

Bupropion

Previously known as amfebutamone (Wellbutrin®, Zyban®, Budeprion® and Buproban®) is an atypical antidepressant that acts as a norepinephrine and dopamine

re-uptake inhibitor and a nicotinic antagonist. Bupropion in general belongs to the chemical class of aminoketones and is similar in structure to the stimulant cathinone, to the anorectic diethylpropion, and to phenethylamines. Initially researched and marketed as an antidepressant, bupropion was subsequently found to be effective as a smoking cessation aid. In 2006 it was the fourth-most prescribed antidepressant in the United States retail market, with more than 21 million prescriptions. Bupropion lowers seizure threshold and its potential to cause seizures was widely publicized. However, at the recommended dose the risk of seizures is comparable to the one observed for other antidepressants. In contrast to many psychiatric drugs, bupropion is an antidepressant of the newer generation with lesser side effects. It does not cause weight gain or sexual dysfunction, and presently has been approved by the US FDA for the treatment of depression ("cocaine blues") associated with ending cocaine use.

Phenelzine

Under the proprietary name Nardil®, this agent appears to be effective with cocaine patients in reducing sleep disturbances and depression, enhancing concentration, and augmenting energy, but requires several weeks before results are obtained. If the patient relapses during this time, the interaction between cocaine and phenelzine can cause a fatal hypertensive crisis due to adrenalin surge.

Desipramine (Norpramin®, Pertofrane®)

This tricyclic antidepressant agent was one of the first medications to be studied as a treatment for cocaine dependence and, as such, is one of the most extensively studied pharmacotherapies for cocaine dependence to date [75]. The rational for its use is that it blocks re-uptake of norepinephrine and to a lesser extent dopamine, thus acting as a specific antianhedonic agent in cocaine-dependent patients, and similar to other antidepressants, it seems to hold the greatest promise in treating depression, even though having a slow mode of action. It seems to ameliorate dysphoria and anhedonia during the post-cocaine crash. Controlled clinical results, however, raise some questions about the efficacy of tricyclic antidepressants in reducing both cocaine craving and usage.

Dopamine Antagonists

Studíes have indicated that haloperidol (Haldol®) and similar dopamine (DA) antagonists (e.g. Flupentiol®) might be contraindicated for longterm treatment of cocaine abuse. It appears that one possibility is that such agents could contribute to enhanced cocaine effects [76]. These findings may also help to partially explain the high prevalence of cocaine abuse in neuroleptic-maintained schizophrenics [77].

Bromocriptine (Parlodel®)

While it is postulated that chronic cocaine use may deplete central dopamine (DA) stores, this could result in supersensitivity of dopaminergic receptors. Thus DA hypofunction induced by cocaine abuse may underlie craving and withdrawal symptoms often observed in recently abstinent cocaine dependent patients. Treatment with bromocriptine, a second generation antidepressant, therefore might reverse dopaminergic deficits induced by cocaine and ameliorate craving and withdrawal. Bromocriptine is an agonist with high affinity for the D2 receptor by directly stimulating the postsynaptic dopamine receptors, thus by-passing the depleted presynaptic dopamine vesicles. It reduces craving for cocaine in certain patients within minutes after administration. However, this drug has well-known side effects, including headaches, sedation, tremor, vertigo, and dry mouth. Furthermore, bromocriptine may itself create drug dependency since it has been demonstrated to be self-administered by laboratory animals. Other side-effects contain a high incidence of gastrointestinal upset with nausea and vomiting and psychotic symptoms. Given its DA agonist properties, this drug is considered for further clinical trials to assess its efficacy for treatment of primary cocaine dependence.

Amantadine hydrochloride (Symmetrel®)

One of the newest compounds to be evaluated in the treatment of cocaine withdrawal reactions is amantadine. This agent increases dopaminergic transmission, but whether the mechanism is dopamine (DA) release, directly effects DA receptors, or DA re-uptake blockade is unclear. Patients receiving this drug do experience, from time to time, Parkinsonian symptoms such as muscular rigidity or impaired reflexes. The most important problems are that the patient exhibits severe dopamine depletion, and the dopamine releaser does not work because there is no dopamine to release. It has been shown to be effective in reducing depression and craving for cocaine when used in combination with the amino acids L-tryptophan and L-tyrosine. A comparison of amantadine and bromocriptine has been published [78], which shows significant improvements and less adverse reactions than seen with bromocriptine.

L-Deprenyl (Seligiline®)

It is an irreversible monoamine oxidase type B inhibitor that specifically inhibits the metabolism of DA. Its present indication is for the treatment of Parkinson's disease. The ability of L-deprenyl to potentiate DA has led to consideration of its use in the treatment of cocaine dependence. In studies, however, there was no difference in cardiovascular effects or drug *liking* when using the cocaine-alone administration or the L-deprenyl-cocaine combination.

Methylphenidate (Ritalin®, Rilatine®, Attenta®, Methylin®, Penid®, Rubifen®)

This drug is a stimulant drug primarily used in the treatment of childhood attention deficit hyperactivity disorder (ADHD). Methylphenidate is a dopamine (DA) agonist with pharmacological properties that include DA release and re-uptake inhibition. A study demonstrated a novel approach to drug development and showed that this class of medications may be useful in the treatment of cocaine dependence [79]. Focalin® is a newer preparation containing only the dextro-methylphenidate, rather than the usual racemic dextro-and levo-methylphenidate mixture of other formulations. A recent way of taking methylphenidate is by using a transdermal patch (Daytrana®).

L-Dopa Ligands (Dopar®, Larodopar®, and Sinemet®)

This is a combination of carbidopa and levodopa, and all dopa ligands are used as a prodrug to increase dopamine levels for the treatment of Parkinson's disease, since it is able to cross the blood–brain barrier, whereas dopamine itself cannot. Once levodopa has entered the central nervous system, it is metabolized to dopamine by aromatic L-amino acid decarboxylase (Fig. 49). Pyridoxal phosphate (vitamine B6) is a required cofactor for this decarboxylation, and may be administered

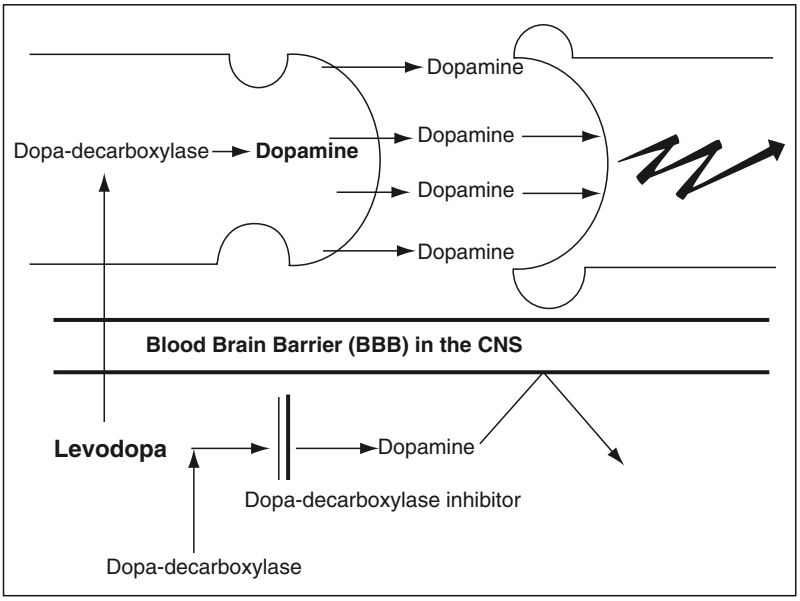

Fig. 49 Because dopamine cannot cross the blood–brain–barrier (BBB) the precursor levodopa is administered, which in combination with an inhibitor of the enzyme decarboxylase, is able to diffuse into the CNS where it is converted into dopamine thus replenishing the deficient vesicles at the nerve terminals

along with levodopa, usually as pyridoxine. However, conversion to dopamine also occurs in the peripheral tissues, i.e. outside the brain. This is the primary mechanism of the adverse effects of levodopa. It is standard clinical practice to co-administer a peripheral DOPA decarboxylase inhibitor – carbidopa or benserazide – and often a catechol-O-methyl transferase (COMT) inhibitor, to prevent synthesis of dopamine in peripheral tissue. Co-administration of pyridoxine without a decarboxylase inhibitor accelerates the extracerebral decarboxylation to such an extent that it cancels the effects of levodopa administration, a circumstance, which historically caused great confusion. For years, these agents were used to treat Parkinson patients by replenishing their supply of dopamine presynaptically. They are less satisfactory in reducing cocaine craving than bromocriptine or amantadine. Furthermore, levodopa agents can produce hallucinations, and they have many of the same side effects as seen with bromocriptine.

Lithium (Lithobid®, Lithonate®, Lithotabs®, Eskalith®)

This compound generally is used in the treatment of bipolar manic-depressive illness. It has been studied as a potential blocker (antagonist) of cocaine effects, especially euphoria, thus avoiding relapse.

Cocaine Antagonists

A variety of medications have been examined for their effectiveness in blocking the reinforcing effects of cocaine. These drugs, including mazindol, fluoxetine, carbamazepine, naltrexone, disulfiram, and the highly potent antagonist 4-iodococaine, have been the subject of study over the past several years. They all have a broad range of pharmacological properties, and differ greatly in primary indication. However, all have been postulated to antagonize the effects of cocaine through pharmacological properties specific to each drug, which might alter neurobiological and reinforcing effects of cocaine. Comparative studies are still pending.

Non-pharmacological Treatment of Cocaine Addiction

Condition Behavioral Therapy (CBT)

Aside from phramacological treatment and based on social learning theory, condition behavioral therapy or CBT, presents another option. Within this theory it is assumed that conditioning presents an important factor in how individuals begin to use and abuse substances and that they learn to do so. The several ways individuals may learn to use drugs include modeling, operant conditioning, and classical conditioning.

Such conditioning can be derived from Pavlov's classical experiments. Pavlov demonstrated that, over time, repeated pairings of one stimulus (e.g., a bell ringing) with another (e.g. the presentation of food) could elicit a response (e.g. a dog salivating). Over time, cocaine abuse may become paired with money or cocaine paraphernalia, particular places (bars, places to buy drugs), particular people (drug-using associates, dealers), times of day or week (after work, weekends), feeling states (lonely, bored), etc. Eventually, exposure to those cues alone is sufficient to elicit very intense cravings or urges that are often followed by cocaine abuse. For each instance of cocaine use during treatment, the therapist and patient do a functional analysis, that is, they identify the patient's thoughts, feelings, and circumstances before and after the cocaine use. Early in treatment, the functional analysis plays a critical role in helping the patient and therapist assess the determinants, or high-risk situations, that are likely to lead to cocaine use and provides insights into some of the reasons the individual may be using cocaine (e.g., to cope with interpersonal difficulties, to experience risk or euphoria not otherwise available in the patient's life). Later in treatment, functional analyses of episodes of cocaine use may identify those situations or states in which the individual still has difficulty coping. CBT can be thought of as a highly individualized training program that helps cocaine abusers unlearn old habits associated with cocaine abuse and learn or relearn healthier skills and habits. By the time the level of substance use is severe enough to warrant treatment, patients are likely to be using cocaine as their single means of coping with a wide range of interpersonal and intrapersonal problems.