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PATHOPHYSIOLOGY AND TREATMENT OF COCAINE DEPENDENCE

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PHARMACOTHERAPY TARGETS IN STIMULANT DEPENDENCE

Pharmacotherapy can help to initiate abstinence and prevent relapse among the estimated 2 million stimulant-dependent users (1). These 2 million dependent users include some of the residual of long-term users from the peak of this epidemic 15 years ago, but a steady stream of new users and casualties is also accumulating. Between 1991 and 1998 the 30-day prevalence of cocaine abuse among eighth, tenth, and twelfth graders had increased more than twofold (1). Casualties from stimulant use also continue to accumulate, cocaine involvement in emergency room accident and violence cases remains prominent, and recent National Institute of Justice figures show that male and female arrestees in major cities display 40% to 80% cocaine-positive urines (2). These emergency room episodes have remained stable after a 78% increase from 1991 to 1994. Now localized epidemics of amphetamine abuse are developing, particularly in the western United States. The dangers associated with stimulant use are enormous and include increased risk of HIV infection, possible detrimental effects on the unborn and newborn, increased crime and violence, as well as medical, financial, and psychological problems. Because of these consequences, the task of identifying, characterizing, and developing treatments is more important than ever.

Models of Treatment: Neurobiological

To initiate abstinence among stimulant abusers, pharmacotherapy can be directed toward the abnormalities that stimulant dependence appears to create in normal neurobiology. This medication role in renormalizing these alterations parallels the role of medications for initiating abstinence from

alcohol or opioids, where pharmacotherapy can reduce the harm from seizures or widespread physiologic withdrawal symptoms. Although discontinuation of stimulant dependence is not associated with severe medical complications, abstinence initiation does produce symptoms of dysphoria (3). These symptoms can be pharmacotherapy targets, and more broadly the disrupted cognition of stimulant abusers can be targeted to facilitate behavioral and cognitive psychotherapies, which have demonstrated efficacy for these disorders. Thus, in addition to abstinence initiation and relapse prevention to stimulant use, surrogate targets include withdrawal symptoms such as craving and dysphoria as well as cognitive impairment, which can result from disrupted neurobiology. Because depressive symptoms are relatively common among stimulant abusers in the early phases of abstinence, antidepressants for stimulant abusers were one of the first interventions studied in controlled trials. Although these medications have a checkered history of failures and successes, some recent data suggest that the depressed stimulant abuser may benefit from antidepressants (4,5). This benefit includes reductions in stimulant abuse as well as the depressive symptoms, and is consistent with the recent findings among depressed alcoholics and older studies in depressed methadone maintained patients (6). However, stimulants may induce a depressive syndrome, and these secondary or drug-induced depressions are less clear targets for pharmacotherapeutic intervention (5,6).

A useful concept in treatment of these patients is renormalization of disrupted neurobiology. Abnormalities in neurotransmitter receptors and transporters that have been noted in animal models have been confirmed in human neuroimaging studies of the dopamine neurotransmitter systems (7,8). Neuroendocrine challenge studies show functional defects consistent with these neuroimaging findings, and norepinephrine systems that stimulants might also disrupt show parallel pharmacologic-challenge abnormalities such as lowered thresholds for yohimbine induction of panic attacks (9–11). These three neurotransmitter systems show

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the direct actions of chronic stimulants, but other neuro-transmitter systems are indirectly affected including glutamate, γ-aminobutyric acid (GABA), and κ opioid systems (12). Abnormalities in any of these systems are appropriate targets for pharmacotherapy and have been targeted by clinical trials using a range of available agents that are reviewed below.

Although reversible abnormalities in neurotransmitter systems offer the potential for renormalization with sub-chronic treatment, maintenance treatment may be essential for irreversible changes or genetic predispositions. Examples of such abnormalities among stimulant abusers have been suggested for the postsynaptic dopamine receptor, which may be irreversibly down-regulated compared to normal individuals and even symptomatically resemble Parkinson's disease. Among candidates for genetic predispositions are polymorphisms in the dopamine transporter (DAT) associated with paranoia such as tandem repeats at the SLC6A3 site (13). Recently, the homozygous 10 tandem repeat, which along with the 9 repeat are the most common variants, has also shown a functional correlate of reduced DAT binding in humans (14). A critical association relevant to cocaine abusers is the up-regulation of the DAT after chronic cocaine in many abusers (7). Those who possess this 10 repeat polymorphism are not likely to have their DAT become up-regulated and therefore be successful candidates for medications that target postsynpatic dopamine targets rather than the dopamine transporter. Thus, patients with identified genetic polymorphisms in the DAT could be given more effectively targeted maintenance pharmacotherapies to prevent relapse.

Abnormalities in cerebral blood flow also appear to be common among stimulant abusers and may contribute to cognitive dysfunction (15,16). The basis for these perfusion defects appears to be a combination of platelet abnormalities leading to "sticky" platelets and vasospasm from repeated vasoconstriction induced by repeated stimulant use (18). The pharmacotherapies developing for stroke including antiplatelet agents such as clopidogrel and vasodilators such as the calcium channel blockers hold promise for this condition.

Finally, a way to sustain abstinence might be pharmacologic blockade with antibodies, enzymes, or receptor antagonists. The dopamine receptor antagonists such as haloperidol for the D2 receptor or Schering 39166 for the D1 receptor have not been successful, although some argument has been made that a partial agonist with its antagonism only expressed at higher doses might be effective (19). The other more peripheral approach is to prevent or at least slow the entry of stimulants into the brain using antibodies to the stimulant or augmenting the enzymes responsible for metabolic disposition of the stimulant. Because rapid entry of stimulants into the brain appears essential for their reinforcing properties, a delay in this entry might be as effective as fully preventing entry by retarding the stimulant in the

bloodstream (3). Although augmenting cholinesterase activity (the enzyme that metabolizes cocaine to an inactive metabolite) remains to be clinically tested, active immunization has been studied in humans. Consistent with the animal studies, humans produced substantial quantities of antibody to an active immunization, but a reduction in cocaine use among outpatients has yet to be tested, to correlate with the reduced self-administration of cocaine observed in the animal studies (20).

CLINICAL ASPECTS OF STIMULANT USE

The rewarding effects of cocaine and amphetamine are influenced by the route of administration because some routes (e.g., intravenous administration) produce more immediate onset of euphoria. The euphoria appears to depend on occupancy of the DAT (21). The preferred method of self-administering cocaine has been snorting and, more recently, smoking. Amphetamines come in a variety of forms (e.g., pill, liquid, or powder form), but are usually taken orally or intravenously. The effects of route of administration and pharmacokinetics was extensively covered in the previous edition of this chapter (2).

Stimulant use may range from low dose to high dose and from infrequent to chronic or binge patterns. Depending on the dosage, pattern, and duration of use, stimulants can produce several drug-induced states that differ in clinical characteristics. Moderate to high doses of stimulants can produce stimulant intoxication that may or may not be pleasant. The intoxicated person may show signs of hyper-awareness, hypersexuality, hypervigilance, and psychomotor agitation. Often the symptoms of stimulant-induced intoxication resemble mania. The intoxicated person should be monitored by the medical staff until the symptoms of intoxication diminish. If the intoxication does not return to baseline level within 24 hours, mania may be present and treatment for manic disorder may be required (3).

With increased dosage and duration of administration, stimulants can also produce a state of mental confusion and excitement, known as stimulant delirium. Delirium is associated with becoming disoriented and confused, as well as anxious and fearful. Extreme medical caution is needed when treating delirium because such symptoms may indicate stimulant overdose. For instance, crack cocaine addicts who overdose need careful monitoring for seizures, cardiac arrhythmias, stroke, and pulmonary complications. Overdose management has been reviewed in detail (22), but a syndrome of hyperthermia and agitation might be most safely managed with high doses of benzodiazepines (23).

During high-dose stimulant use, often seen during binge episodes, individuals can experience stimulant-induced psychosis characterized by delusions, paranoid thinking, and stereotyped compulsive behavior. When they are delusional, close clinical monitoring is essential and it may be necessary

to employ short-term treatment with neuroleptics to ameliorate the psychosis. It is more common for amphetamine than cocaine to induce psychosis, perhaps due to the difficulty in maintaining high chronic levels of cocaine in the body. Also, stimulant-induced psychosis in humans may be related to the dose and duration of administration of amphetamine, although cocaine psychosis and paranoia may be related to psychiatric predisposition (24).

Stimulant withdrawal, which occurs following cessation of cocaine or amphetamine use, can produce a wide range of dysphoric symptoms. Following binge use, individuals may initially experience a "crash" period, which is characterized by symptoms of depression, anxiety, agitation, and intense drug craving, although controlled studies have shown minimal withdrawal symptoms (3,8).

Treatment of stimulant abuse requires a comprehensive assessment of the patient's psychological, medical, forensic, and drug use history. Moreover, because information obtained from chemically dependent persons may be incomplete or unreliable, it is important that the patients receive a thorough physical including blood and supervised urine samples for analysis. The clinician needs to be aware that polydrug abuse is common. Patients may ingest large amounts of one or more drugs at potentially lethal doses, and therefore it is important that the physician be aware of the dangers of possible drug combinations, such as cocaine and alcohol or heroin.

Pharmacologic intervention may be necessary during stimulant-induced drug states. For instance, neuroleptics may be useful in controlling stimulant-induced psychosis or delirium, and during withdrawal when depression may set in, antidepressants may be an appropriate choice for treatment medication. Treatment medications can be given on an inpatient or outpatient basis. However, if medications are used for outpatient treatment, it is critical to warn the patient of the potential adverse interactions between cocaine and the prescribed treatment medication. For instance, high blood pressure could result from the release of epinephrine by cocaine combined with the reuptake blockade by the tricyclic (25), although later in the course of treatment tricyclics decrease the sensitivity of the postsynaptic adrenergic receptors. Finally monitoring of treatment is essential using urine toxicologies as well as self-reports. The frequency of monitoring may be as infrequent as weekly, but three times weekly is optimal. There appears to be no advantage to quantitative over simple qualitative results based on typical cutoffs such as 300 ng/mL of benzoylecgonine for cocaine use in routine clinical practice.

HUMAN TESTING PARADIGMS FOR NEW MEDICATIONS

Human Laboratory

The human laboratory setting in which cocaine or amphetamine is administered to volunteer subjects has been a critical paradigm for testing potential pharmacotherapies for stimulant dependence (12,25,26). Variations on this paradigm have used visual, tactile, aural, or cognitive cues to induce craving for these abused substances. In both experimental settings, the outcome measures have been subjective responses such as euphoria, unpleasant feelings or craving itself, as well as estimates of how much the drug is worth to the participant (e.g., dollar value). The induction of craving for more cocaine after a small to modest dose of cocaine is called the priming effect, and modulation of this priming effect can be an important role for a treatment medication in reducing relapse (27). This reduction in relapse would occur by preventing a "slip," that is a single use of cocaine in a patient who wants to remain abstinent, from leading into a full relapse to binge cocaine usage.

To more precisely operationalize this human laboratory model, self-administration has been introduced. In that paradigm the subject can self-administer cocaine or amphetamine repeatedly within a range dictated by medical safety considerations. The subject is offered the alternative of getting cocaine or various other rewards that have a range of monetary values. The subject is thereby asked not only to estimate a worth of the cocaine, but also to actually choose to get that amount or to get the cocaine. In these paradigms the behavior of drug taking can be more clearly approximated and a medication that might block the effects of cocaine could be detected. This blocking effect would presumably lead the subject to prefer the alternative reward over the cocaine after the first test dose, when the medication is present, because the reinforcing effects of cocaine would be reduced (12). Although this model has theortical appeal and has shown the expected subject behaviors with various doses of cocaine, it has yet to be tested with an appropriate medication to judge its sensitivity for blocking agents.

In all of these paradigms, the key outcome of cocaine or amphetamine interactions with potential pharmacotherapies yields not only surrogate efficacy data, but also medical safety data. Cardiovascular measures in particular can be carefully monitored after both acute and subchronic dosing with potential medications. The baseline effects of these treatment medications can be assessed in escalating dose regimes, and then dose–response evaluations using escalating doses of cocaine or amphetamine can be examined. Subjective responses may also be important to assess dysphoric interactions between the medication and the abused drugs. These reactions might help in reducing stimulant abuse, although they might also discourage compliance with the medication. Overall, this is a powerful paradigm for medication development because of its potential to inform the clinical trials process with information about how the outpatients in a trial are likely to respond to the new medication, when a study participant uses a stimulant. Its utility as a rapid screening procedure for eliminating medications from further outpatient testing has yet to be demonstrated, but

this may be a future use of these highly controlled paradigms as we obtain gold standard agents with demonstrated efficacy in outpatient trials.

Neuroimaging

A newer technology for human laboratory assessment of potential medications is neuroimaging of either functional activity or receptor and transporter occupancy (28). Functional activity can involve either cerebral blood flow (CBF) or metabolic activity using fluorodeoxyglucose (FDG). The use of FDG as a medication development strategy has been examined in a recent study of selegiline combined with cocaine administration. In this study, selegiline reduced the euphoria from acute cocaine administration, and positron emission tomography (PET) imaging using FDG showed that the cocaine-induced changes in metabolic activity were blocked by the administration of selegiline (29). This surrogate marker provided an interesting correlate of the attenuation of cocaine's subjective effects, because other outpatient work has suggested that selegiline might reduce cocaine abuse in outpatients. Because similar studies of subjective effects alone have not had corresponding predictive validity for outpatient efficacy, these neuroimaging measures may have promise as a more rapid screening tool for medications.

Another medications development approach using neuroimaging focuses on the CBF defects that have been observed in cocaine abusers and on the neuropsychological deficits that persist even during sustained abstinence (6,15, 17). As reviewed below, these CBF defects may be responsive to pharmacotherapy. The therapeutic implication is that by resolving these CBF defects, cognitive functioning might improve, and the response to cognitive behavioral therapies also might be enhanced.

Outpatient Randomized Clinical Trials

Outpatient clinical trials remain the standard approach to assessing efficacy of a medication. Although many principles of conducting randomized placebo-controlled clinical trials in psychopharmacology apply to these studies, some specific considerations are relevant to outcome measures that are not found in other areas. Urine toxicology is a most informative outcome that can be analyzed with both quantitative and qualitative approaches. The urines are typically obtained three times per week for maximum sensitivity to repeated stimulant use based on the duration that detectable metabolite levels remain after use. Analyses are most frequently done with cutoff scores of 300 ng/mL, for example, with the cocaine metabolite benzoylecgonine, with any level above this being considered an indication of cocaine use within the last 3 days. More complex analyses have been proposed using quantitative levels either directly with gas chromotography–mass spectroscopy for quantitation or immunoassays for semiquantitation. This semiquantitation

can be combined with self-reported use and compared to urine levels obtained prior to the urine in question to estimate new use of cocaine, because with three times weekly toxicologies a heavy daily cocaine abuser can stop using for 2 or 3 days and yet still have a positive urine (30) (e.g., positive on Monday and Wednesday when the last use was on Sunday). Although the goal of treatment is often complete abstinence, the sensitivity of these urine tests can be enhanced by these data manipulations. Thus, self-reported decreases in stimulant use may be important as a treatment outcome even when the goal may be abstinence initiation. Treatment retention is also critical in getting toward this goal of abstinence initiation, in order to keep the patient available for intervention.

In these outpatient studies, relapse prevention is a conceptual outcome that follows abstinence initiation. Relapse as defined by recurrent use or dependence after "sustained abstinence" first requires a definition of sustained abstinence, particularly among the binge users of stimulants. These patients may use weekly or even less often in binges that last up to several days. Although meeting the criteria of the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-IV) for stimulant dependence, the periods of nonuse can manifest reasonable psychosocial functioning, yet each time the patient returns to a binge this return is not a relapse. Simple definitions of sustained abstinence can just be defined by a period of cocaine- or amphetamine-free urines that lasts three, four, or perhaps ten times longer than the typical inter-binge interval. For current investigations, an important prognostic stratification is evolving based on sustained abstinence; patients who are abstinent during the 2 to 5 weeks before entering a medication trial have better treatment outcomes than those who continue to use up to their entry into treatment (31). Longer-term relapse prevention has also been an area where psychotherapy may synergize with pharmacotherapy (32). For example, sustained abstinence with desipramine treatment for cocaine dependence was enhanced by relapse-prevention cognitive behavioral therapy when examined at 6 and 12 month follow-up. Relapse was significantly higher after attaining abstinence with the medication alone than with both medication and the behavioral therapy.

SPECIFIC MEDICATIONS

A large number of medications have been used for a variety of cocaine-related effects, including treatment of cocaine withdrawal or cocaine craving, and initiation and maintenance of abstinence. Although many of these medications have appeared to be promising in open trials, randomized, placebo-controlled clinical trials have not shown any medications to have substantial efficacy for cocaine dependence. Many studies have included small sample sizes and have been hampered by large dropout rates. Diagnostic criteria

have varied across clinical trials (some studies enroll patients meeting diagnostic criteria for cocaine dependence or for cocaine abuse, and others do not specify patient diagnosis). Many larger studies have examined patients with primary opiate dependence on methadone maintenance. Although these patients tend to be more available for follow-up because of their need to report to a clinic daily for methadone treatment, it is likely that they are different from patients with primary cocaine use disorders. Therefore, results obtained in studies enrolling methadone-maintained cocaine abusers may not apply to other patient groups. Outcome variables differ among clinical trials, making it difficult to determine a medication's effectiveness. Studies that utilized self-reports without confirmation by urine toxicology screen may not be reflective of cocaine use by study participants.

Antidepressants

Desipramine, a tricyclic antidepressant agent, was one of the first medications to be studied as a treatment for cocaine dependence. It is one of the most extensively studied pharmacotherapies for cocaine dependence to date (4). The initial study of desipramine suggested its efficacy based on self-report primarily, and two subsequent studies in methadone-maintained samples based on urine toxicology found no difference from placebo (33–35). A large clinical trial examined the efficacy of desipramine and psychotherapy, alone and in combination, as a treatment for ambulatory cocaine abusers (32). In this 12-week, double-blind, placebo-controlled trial, 139 subjects were assigned to one of four conditions: relapse prevention therapy plus desipramine, clinical management plus desipramine, relapse prevention plus placebo, and clinical management plus placebo. The mean dose of desipramine was 200 mg daily and was adjusted by a nonblinded psychiatrist in response to plasma concentration (target ranges 300 to 750 ng/mL) and side effects. All groups showed significant improvement in treatment retention and a reduction in cocaine use at 12 weeks, but there were no significant main effects for psychotherapy, pharmacotherapy, or the combination. Lower severity patients (cocaine use 1 to 2.5 g/week) had improved abstinence initiation when treated with desipramine. Desipramine was significantly more effective than placebo in reducing cocaine use during the first 6 weeks of treatment. Depressed subjects had a greater reduction in cocaine use than nondepressed subjects and had a better response to relapse prevention therapy. This finding of a desipramine response among depressed patients was confirmed among the depressed patients on methadone. A subsequent study by Nunes et al. (5) also found that depressed cocaine abusers on methadone had a significant reduction in cocaine use on imipramine, but not placebo. They did not find a significant effect in the nondepressed patients. Finally, a recent study with desipramine in methadone- and buprenorphine-maintained cocaine- and opioid-dependent patients found a re-

duction in both opioid and cocaine abuse with desipramine (36). A recent report of desipramine in depressed cocaine abusers found no difference from placebo; however, those patients whose depression remitted also showed a substantial reduction in cocaine use (37). Thus, these tricyclic antidepressants do not have well-demonstrated utility even in the depressed cocaine abusers, who can be a substantial subgroup comprising up to 40% of those presenting for treatment (3,6).

Several well-controlled human laboratory and outpatient clinical trials with fluoxetine have been conducted in patients with cocaine use disorders. A double-blind, placebo-controlled, cocaine administration study examined the interaction of cocaine with fluoxetine at 0, 20, 40, or 60 mg daily on an ascending schedule (38), and found that the 40- and 60-mg doses of fluoxetine decreased subjective effects of cocaine. Fluoxetine has been utilized in outpatient clinical trials in both methadone-maintained, cocaine-dependent patients and in patients with primary cocaine use disorders. An open study in methadone-maintained, cocaine-dependent patients found that fluoxetine at 45 mg daily significantly reduced self-reported use and quantitative urine benzoylecgonine concentrations during 9 weeks of treatment (39). More recently, fluoxetine has not reduced cocaine positive urines more than placebo in either methadone-maintained or primary cocaine abusers (40). The consensus of these studies is that fluoxetine may not have a clinical role among unselected cocaine abusers, and side effects have limited its use in several studies.

Bupropion is a second-generation antidepressant that enhances dopaminergic and noradrenergic transmission, but has little effect on serotoninergic neurotransmission. Although a pilot study suggested efficacy, a large multicenter study in methadone-maintained patients showed little benefit in cocaine dependence (41).

Dopaminergic Agents (DA)

The most widely accepted explanation of cocaine-induced euphoria is that dopamine reuptake inhibition results in increased extracellular dopamine concentration in the mesolimbic and mesocortical reward pathways in the brain (42). This basis for euphoria has suggested that dopamine antagonists might reduce cocaine use, but few human laboratory studies have supported their use, and controlled outpatient trials with both D1 and D2 antagonists have not been supportive. Although a laboratory study suggested attenuation of cocaine effects by the D1 antagonist Schering 39166, a multisite outpatient trial found no dose response and no difference from placebo in cocaine use (43; Ko, personal communication, 1999). The D2 antagonists such as haloperidol and flupenthixol have had minimal effects on euphoria in human cocaine administration studies (44), and flupenthixol has not been superior to placebo in an outpatient trial (45).

Because relative DA hypofunction induced by cocaine abuse may underlie craving and withdrawal symptoms that are often observed in recently abstinent cocaine-dependent patients (3), DA agonists may be of use. Bromocriptine is an agonist with high affinity for the D2 receptor. In human studies, pretreatment with either bromocriptine 2.5 or 5 mg 2 hours prior to cocaine administration had no effect on cocaine euphoria (46). Although early work supported its use, even in an early double-blind clinical trial, bromocriptine at 5 to 7.5 mg daily was poorly tolerated, with high dropout rates (47). In another small double-blind, placebo-controlled trial Moscovitz et al. (48) gave bromocriptine 1.25 mg three times daily or placebo to cocaine-abusing patients presenting to an emergency room for minor medical complaints. They found no difference in retention (bromocriptine group 43%, placebo group 31%), but those randomized to bromocriptine had more urine toxicology screens negative for cocaine (67%) than those randomized to placebo (31%). Cocaine administration studies have found a lack of effects with pergolide (49). A placebo-controlled outpatient study of pergolide found no difference in cocaine use and significant side effects, in spite of early pilot work in 21 patients suggesting good responses in 16 of 21 patients (50). Most recently, the D1 agonist ABT431 has been examined in human cocaine administration studies and found to reduce cocaine-induced craving (51). This compound is only available intravenously, but this offers promise for related compounds such as the D3 partial agonist recently reported in the animal laboratory (19).

Amantadine increases dopaminergic transmission, but whether the mechanism is DA release, direct effects on DA receptors, or DA reuptake blockade is unclear. One study examined the effects of acute amantadine (200 or 400 mg) and chronic amantadine (100 mg twice daily for 4 days) followed by insufflation of cocaine 0.9 mg/kg (52). Although the acute 200-mg dose of amantadine was associated with a decrease in cocaine "high," chronic administration of amantadine 100 mg twice daily was associated with increased "high" in male subjects after cocaine administration. The effectiveness of amantadine was evaluated in a double-blind, placebo-controlled trial in which 42 patients in a day treatment program were randomized to amantadine 100 mg twice daily ($n = 21$) to be taken over 10 days or placebo ($n = 21$). Urine toxicology screens showed that those who had received amantadine were significantly more likely to be free of cocaine ($p < .05$) at the 2-week and 1-month follow-up visits (53).

L-deprenyl is a monoamine oxidase type B inhibitor that specifically inhibits the metabolism of DA. A study in five human volunteers examined the effects of 10 mg L-deprenyl alone and in combination with cocaine, but found no attenuation of cocaine effects (54). More recently, it was found to attenuate some subjective effects of cocaine, and an outpatient trial showed reduced cocaine use reported in comparison to placebo (29; Vocci, personal communication, 2000).

Methylphenidate (MP) is a stimulant and DA agonist primarily used in the treatment of childhood attention-deficit/hyperactivity disorder. MP is a DA agonist with pharmacologic properties that include DA release, and it has similar levels of binding to the DAT as cocaine. Grabowski et al. (55) have reported that it does not increase cocaine use and retains patients better than placebo, but have not shown a reduction in cocaine use compared to placebo.

Mazindol is a DA reuptake inhibitor that is without abuse liability and it has been suggested that it might antagonize the effects of cocaine as a treatment. A report on the effects of cocaine alone and in combination with mazindol at 1 or 2 mg orally in cocaine abusing volunteers found that the combination significantly increased heart rate and blood pressure (56). Mazindol did not alter the subjective effects of cocaine. One 12-week, double-blind, placebo-controlled clinical trial of mazindol 2 mg daily in cocaine-dependent subjects reported no difference from placebo (57). Mazindol was also not well tolerated, with 16 of 33 patients dropping out, and the average length of treatment was 5 weeks. A similar trial in methadone maintained patients found limited efficacy for those patients who had been cocaine abstinent for at least 2 weeks before starting mazindol (58).

Nonspecific Anticraving Agents

A number of other agents have been tested to reduce the desire or craving for cocaine. The rationales have broadly involved mechanisms such as sensitization and kindling as well as neurotransmitter systems that are indirectly affected by cocaine such as the opioid, excitatory amino acid/glutamate, and GABAergic systems. For most of these approaches, outpatient clinical trials have been quite limited. Medications include GABA agents such as baclofen, opioid antagonists such as naltrexone, calcium channel blockers such as nifedipine, antikindling agents such as carbamazepine, and disulfiram. Finally, stress responses and the associated elevation of cortisol have been considered as potentially important in cocaine craving induction and as a therapeutic agent. However, a cocaine administration study showed no reduction in cocaine effects or self-administration with the cortisol synthesis inhibitor ketoconazole in spite of significant reductions in cortisol levels (59).

Carbamazepine (CBZ) is an anticonvulsant medication hypothesized to have potential as a treatment for cocaine craving and abuse because of its ability to block cocaine-induced "kindling" in rodents. A double-blind, placebo-controlled, crossover study of the interaction of 400 mg of CBZ daily for 5 days with cocaine found no effects on subjective response to cocaine (60). A double-blind, placebo-controlled study in outpatients included a 20-day, controlled, fixed-dose (CBZ 200 mg or 400 mg or placebo)

trial in 30 volunteers and found that cocaine use was unchanged (61). Another study in 183 cocaine abusers randomized to CBZ 400 or 800 mg daily or placebo showed that CBZ at 400 mg was associated with a significant decrease in cocaine-positive urines and a reduction in cocaine craving (62). However, three other double-blind, placebo-controlled studies with CBZ treatment in over 150 subjects found no significant difference in cocaine use, cocaine-positive urine samples, or depressive symptoms measured by the Beck Depression Inventory (63–65). Plasma CBZ levels of 5.6 ± 0.8 µg/mL were achieved by week 4 in these studies. Thus, confidence in this medication has waned.

Naltrexone is an opioid antagonist that has been examined as a treatment agent for cocaine abuse. One study examined the effects of cocaine after 10 days of treatment with naltrexone 50 mg or placebo in a double-blind, randomized, within-subjects design (66). Some cocaine-induced subjective effects were less during naltrexone than placebo administration. A placebo-controlled outpatient study of naltrexone found no efficacy (67).

The calcium channel blockers and antagonists of glutaminergic function have also been examined as anticraving agents and protective agents to minimize cardiovascular cerebral damage from cocaine. The calcium channel antagonist nifedipine has been studied and shows some promise (68). Nimodipine showed a reduction in the effects of intravenous cocaine as well as reductions in acute cocaine-related cardiovascular toxicity, but lamotrigine did not reduce cocaine effects in a similar placebo-controlled crossover study (69,70). Memantine, a glutamate inhibitor, showed no efficacy in reducing cocaine effects acutely (71). Outpatient placebo-controlled studies have not been done with these agents, however.

Much enthusiasm has developed for the use of agents targeting the GABA system, particularly for vigabatrin, which antagonizes the breakdown of GABA (72). Unfortunately, this agent is not available in the United States, and its side effects of bitemporal hemianopsia may preclude its use in cocaine abusers (73). However, baclofen, which is a direct agonist for the $GABA_B$ receptor, has shown some reduction in cocaine self-administration in animals and some utility in reducing cocaine abuse among humans (74). No other controlled trials have been published with this or related GABA agents, but several have gotten preliminary screenings in the National Institute on Drug Abuse (NIDA) medications development program including tiagabine, which also enhances GABA levels (Vocci, personal communication, 2000).

Disulfiram is an aldehyde dehydrogenase inhibitor used in treating alcoholism, a common coexisting problem among cocaine abusers. One study in six cocaine-dependent volunteers examined the effect of disulfiram 250 mg on responses to intranasal cocaine (2 mg/kg) using a randomized double-blind, placebo-controlled design (75). Although disulfiram induced no significant differences in co-

caine "high," it decreased craving for cocaine. Plasma cocaine concentration following cocaine administration was significantly greater while on disulfiram, and this may have contributed to the decreased craving and increased dysphoria observed in some subjects. Carroll et al. (76) found that cocaine use was significantly reduced in the disulfiram group compared to psychotherapy alone, with patients who abused both alcohol and cocaine. The patients reported a significantly lower percentage of cocaine use days and fewer days of cocaine use, and fewer positive urine screens for cocaine were observed.

In surveys of cocaine abusers, 65% have reported significant problems in concentration and 57% reported memory problems, and formal testing suggests some sustained abnormalities in memory and concentration among abusers (3, 16). Initial studies of recovering cocaine-dependent patients have revealed impairments of short-term memory, attention, and complex psychomotor and simple motor abilities, but the data are limited (16,77). Reaction time, motoric signs of central nervous system (CNS) dysfunction, and EEG evidence of residual CNS hyperexcitability may also persist (78).

These problems may be associated with structural or functional brain damage caused by cocaine including strokes (16). Structural imaging using computed tomographic scanning and magnetic resonance imaging (MRI) have shown enlarged ventricles and sulci in cocaine abusers (79). Functional neuroimaging studies have shown focal reductions in regional cerebral blood flow (rCBF) among chronic cocaine abusers (15–17). These defects also appear to be persistent for several weeks of abstinence at least, and can be associated with neuropsychological deficits (15–17,80). The ischemic damage from cocaine can lead to neuronal degeneration, as suggested by phosphorus magnetic resonance spectroscopy (^{31}P-MRS), in which abstinent cocaine abusers showed abnormally high levels of phosphomonoesters and low levels of nucleotide triphosphates compared to normals (81).

The etiology of decreases in rCBF following cocaine may involve vasoconstriction (82) and platelet abnormalities. The vasoconstriction may respond to calcium channel blockers (83). Abnormal platelets may produce thrombosis in cerebral vessels and produce blood flow alterations (18). In autopsy studies platelet-rich coronary thrombi (sometimes in otherwise normal vessels) and accelerated atheromatous lesions are found and could be ascribed to platelet activation and platelet α-granule release (16). Because platelet granule release appears to be completely inhibited by aspirin under *shear* conditions (analogous to flowing blood), and aspirin prevents thrombotic complications, a preliminary test of 4 weeks of aspirin therapy led to a 50% improvement in cerebral perfusion (16). In a placebo-controlled study that has just been completed, aspirin significantly reduced perfusion defects on single photon emission computed tomography (SPECT) imaging (84,85).

Peripheral Blocking Agents Targeting Cocaine Itself

Although the simplest peripheral blocking approach of passively injecting polyclonal antibodies to cocaine into a human might be useful for cocaine overdoses, these antibodies would not last very long and might be of limited use as a sustained treatment. For any type of relapse prevention, the immune response elements must remain at relatively high levels for periods of several weeks or months, which is best done by active immunization (86). However, three other approaches using catalytic antibodies, monoclonal passive antibodies, or injections of butrylcholinesterase have some promise (87). With all these peripheral cocaine-blocking agents, the amount of cocaine entering the brain is partially blocked or its rate of entry is reduced. Either of these effects can cause a very significant reduction in the high or rush from cocaine. All four of these approaches can also be combined and used together with the pharmacotherapies described above. The only approach that has been tested in humans is active immunization (86). The initial animal studies showed excellent production of a highly specific antibody to cocaine. With active immunization the amount of inhibition of cocaine entering the brain ranged from 30% to 63% at 30 seconds after cocaine injection in rats. This amount of inhibition was sufficient to extinguish cocaine self-administration in the rat model.

In the initial human study of this vaccine, it was well tolerated with virtually no side effects using a dose of 1,000 μg given with two booster injections over a 3-month period (88). The vaccine produced substantive quantities of antibody that was related to both the dose of vaccine and the number of booster injections. Thus, further studies of its potential efficacy in relapse prevention for abstinent cocaine abusers appear warranted.

PSYCHOTHERAPIES

Professional Psychotherapy vs. Drug Counseling

Because of the limited efficacy of pharmacotherapy, the success of behavioral and psychotherapies is important to consider. Two major approaches have been evaluated. First, the use of professional therapies such as cognitive behavioral therapy and supportive expressive therapies has been examined. Second, contingency management as a form of behavioral therapy has gotten much attention and reasonable success. These therapies have now been extensively studied and are increasingly being examined as treatments that might be complemented by emerging pharmacotherapies. However, nonprofessional drug counseling also holds much promise and many be more readily available to community programs.

The most extensive examination of psychotherapy for cocaine dependence has been the NIDA Collaborative Cocaine Treatment Study. It was a large, multisite psychotherapy clinical trial for outpatients who met the DSM-IV criteria for cocaine dependence. For 480 randomized patients, four treatments were compared over an 18-month period. All treatments included group drug counseling. One treatment also added cognitive therapy, one added supportive-expressive psychodynamic therapy, and one added individual drug counseling. The final group had drug counseling alone. Two specific interaction hypotheses, one involving psychiatric severity and the other involving degree of antisocial personality characteristics, were examined, but no major findings related to these hypotheses have been found (88, 89).

All of the therapies were manual guided and treatment was intensive, including 36 possible individual sessions and 24 group sessions for 6 months. Patients were assessed monthly during active treatment and at 9 and 12 months after baseline. Primary outcome measures were the Addiction Severity Index–Drug Use Composite score and the number of days of cocaine use in the past month. Compared with the two psychotherapies and with group drug counseling (GDC) alone, individual drug counseling plus GDC showed the greatest improvement on the Addiction Severity Index–Drug Use Composite score. Individual group counseling plus GDC was also superior to the two psychotherapies on the number of days of cocaine use in the past month. Hypotheses regarding the superiority of psychotherapy to GDC for patients with greater psychiatric severity and the superiority of cognitive therapy plus GDC compared with supportive-expressive therapy plus GDC for patients with antisocial personality traits or external coping style were not confirmed. Thus, compared with professional psychotherapy, a manual-guided combination of intensive individual drug counseling and GDC showed promise for the treatment of cocaine dependence (90).

Cognitive Behavioral Therapy (CBT)

In spite of these overall discouraging results, cognitive behavioral treatments have been among the most frequently evaluated psychosocial approaches for the treatment of substance use disorders and have a comparatively strong level of empirical support (91,92). To date, more than 24 randomized controlled trials have evaluated the effectiveness of cognitive behavioral relapse prevention treatment on substance use outcomes among adult tobacco smokers and alcohol, cocaine, marijuana, opiate, and other types of substance abusers (93). Overall, these studies suggest that the average effect size for CBT compared with control or comparison conditions is 0.36 (Feingold, unpublished data/APA presentation), which is consistent with a moderate effect. Review of this group of studies suggests that, across substances of abuse but most strongly for smoking, there is good evidence of the effectiveness of CBT compared with no-treatment

controls (93). This body of literature also suggests that outcomes in which CBT may hold particular promise include reduced severity of relapses when they occur, enhanced durability of effects, and patient-treatment matching, particularly for patients at higher levels of impairment along dimensions such as psychopathology or dependence severity. A review of this series of studies can be found in Carroll (93).

To help cocaine-dependent individuals meet the treatment goal of abstinence and relapse prevention, CBT treatment has two critical components. The first is a thorough *functional analysis* of the role cocaine and other substances play in the individual's life. A functional analysis is simply an exploration of cocaine use with respect to its antecedents and consequences. The second critical component of CBT is skills training. In CBT, a substantial portion of every session is devoted to the teaching and practice of coping skills; in fact, 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 more healthy skills and habits. Other important features of CBT are fostering the motivation for abstinence, teaching coping skills, changing reinforcement contingencies, fostering management of painful affects, and improving interpersonal functioning.

In a study comparing supportive therapy to CBT for pharmacotherapy of cocaine dependence, 121 individuals meeting DSM-III-R criteria for cocaine dependence were randomly assigned to one of the four treatment conditions: (a) CBT in combination with desipramine, (b) CBT plus placebo, (c) clinical management (ClM) plus desipramine, and (d) ClM plus placebo (33). Cocaine outcomes were comparable whether the patient received CBT or ClM, or whether the patient received desipramine or placebo, but patients with more severe cocaine use were retained longer in treatment, attained longer periods of abstinence, and had fewer urine screens positive for cocaine when treated with CBT compared with ClM. CBT also was more effective than supportive ClM in retaining depressed subjects in treatment and in reducing cocaine use (94). Thus, CBT has been useful for medication development as a platform for clinical trials because it meets the guidelines for an effective platform. Specifically, it is strong enough to hold patients in treatment, but not so strong as to eliminate the possibility for any medication effects. As counterexamples, treatments such as clinical management tend to be too weak to hold patients, although day treatments tend to produce very high rates of abstinence without any medications, but can serve as excellent means to inducing initial abstinence.

Contingency Management Procedures

Contingency management (CM) procedures are based on a behavioral perspective of drug abuse, which views drugs as powerful reinforcers maintaining high rates of behavior aimed at administering the drugs, even in the absence of physical dependence (95). In substance abusers, drugs can therefore be seen as being the predominant reinforcers exerting control over a large portion of these individuals' behavioral repertoire, whereas in nonsubstance abusers more socially acceptable reinforcers influence behavior. Thus, the goal of drug abuse treatment is to decrease behavior maintained by drug reinforcers and increase behavior maintained by nondrug reinforcers. CM procedures are one method of accomplishing this goal, by presenting rewards or incentives contingent upon documented drug abstinence (positive contingencies), withdrawing privileges contingent upon documented drug use (negative contingencies), or a combination of the two.

Higgins and colleagues (95–97) have demonstrated that CM procedures in combination with a community reinforcement approach (CRA) facilitate initial abstinence in primarily cocaine-dependent persons. In the first, 12-week study (95), the CM procedure consisted of vouchers with a monetary value, which were presented upon evidence of drug abstinence (i.e., cocaine-free urine) during weeks 1 to 12. The vouchers increased in value for every consecutively drug-free urine and were exchangeable for client-therapist agreed-upon retail items and activities related to treatment goals. Treatment retention was significantly higher in the behavioral treatment than standard drug counseling group. In addition, 85% of clients receiving the behavioral treatment achieved at least 3 weeks of abstinence as compared to 33% of clients receiving standard drug abuse counseling. In the second study (96), the CM procedure was modified, in that vouchers exchangeable for goods and services in weeks 1 to 12 and lottery tickets in weeks 13 to 24 were presented contingent upon documented drug abstinence. As before, treatment retention was significantly higher in the behavioral treatment than standard drug counseling group. Similarly, 68% and 42% of the clients in the behavioral treatment group achieved at least 8 and 16 weeks, respectively, of continuous cocaine abstinence as opposed to 11% and 5% in the standard drug abuse counseling group. In the third, 24-week study (97), cocaine-dependent individuals were randomized to receive either behavioral treatment without incentives or behavioral treatment with incentives (i.e., vouchers exchangeable for goods and services). The group that received the incentives showed significantly greater treatment retention (75% vs. 40%) and longer duration of continuous abstinence (11.7 vs. 6.0 weeks) than the group not receiving the incentives. Overall, the findings of these studies suggest that incentives contingent on drug abstinence can be a powerful intervention for facilitating cocaine abstinence in primary cocaine abusers, although separating the CRA effects has not been done.

This voucher system also has been examined in a 12-week clinical trial for its ability to facilitate cocaine abstinence in methadone-maintained cocaine abusers (98,99). The contingency group subjects achieved significantly longer dura-

tions of sustained abstinence than yoked-controls (mean of 5.0 vs. 0.8 weeks, respectively), with 47% of contingency subjects achieving at least 7 weeks vs. 6% of controls achieving at least 2 weeks of sustained cocaine abstinence. These findings suggest that vouchers also can be used as incentives for drug abstinence in opioid-dependent cocaine abusers using a CM procedure similar to that employed by Higgins et al. (97).

There are also problems with CM. One issue with CM procedures is that the therapeutic effects tend to be impermanent following withdrawal of the intervention. This issue of continued efficacy after stopping medications has been addressed in a very limited way, mostly due to the lack of medications showing equivalent efficacy to these contingency approaches (32). Also, there are no mechanisms available to support CM in standard clinical programs, although some new approaches are being developed (100,101). Because vouchers are used to support treatment goals, therapists must work with patients to evaluate appropriate use of the vouchers, and treatment staff generally must assist in making voucher purchases. These restrictions impose considerable program costs over and above the costs of the vouchers. The delay between the time the reinforcement (purchase of goods or services) is provided and the time that the behavior being reinforced (abstinence, as evidenced by a drug-free urine) occurs may decrease the value to the patient (but not the actual program cost) of the reinforcement. The efficacy of CM in studies with cocaine-dependent patients also appears to be considerably more modest at best than in the earlier studies. Iguchi and his colleagues (102) compared voucher-based CM used to reinforce either drug-free urine samples (UA group) or treatment plan tasks (TP tasks) and a no-voucher standard treatment group (STD) during methadone maintenance treatment. The value of the vouchers was set considerably lower than in other studies of CM and did not increase in value for successive drug-free urine samples or completion of therapeutic tasks. The authors also did not use the CRA that Higgins has used, although their TP intervention included many of the CRA elements. There were no significant main effects of treatment group on rates of drug-free urine samples. Rates of drug-free urine samples remained relatively unchanged in either the UA or STD groups, whereas they increased over time in the TP group. Finally, CM is not effective for all patients—for example, 10 of 19 (53%) CM-treated methadone-maintained patients failed to achieve more than 3 consecutive weeks of cocaine abstinence in the study reported by Silverman and his colleagues (98,99), and resumption of drug use following discontinuation of CM is also a problem. Although increasing the value, schedule, or duration of the vouchers may lead to higher and more sustained rates of abstinence (103), alternatives to CM should also be explored. Considering that drug-dependent patients continue illicit drug use despite extremely high immediate and longer-term costs, increasing patient internal

motivation may be more cost-effective than increasing the value of the vouchers or monetary rewards for abstinence. Of additional concern is the possibility that failure to earn vouchers may contribute to demoralization and a lack of perceived self-efficacy for succeeding in stopping drug use and thus contribute to a cycle of drug use and failure.

In summary, despite its promise, there are a number of limitations of CM for the treatment of patients with cocaine dependence: (a) CM is of limited efficacy in this population. (b) CM is labor intensive and difficult to implement. (c) CM is costly and not supported by current funding mechanisms. (d) The failure to obtain vouchers in CM may contribute to demoralization. (e) There is a possible rebound in drug use or dissipation of effects after discontinuation of CM.

CM's potential utility as a platform for pharmacotherapy has yet to be fully explored, but recent reviews suggest it may have a modest effect size of 0.25 and that various approaches can be used to apply it in community settings (101,104).

SUMMARY

No medications are currently approved by the Food and Drug Administration (FDA) for cocaine dependence, but we have developed several leads for medications based on our understanding of the neurobiology and clinical phenomenology of stimulants. Based on neurobiological abnormalities in dopamine receptors and transporters after chronic stimulant use, studies have examined both dopamine agonists and antagonists, but not shown clinical efficacy. Based on clinical phenomenology, antidepressants have been tried in depressed cocaine abusers who may reduce their cocaine use with desipramine, other tricyclics, serotonin reuptake inhibitors, and bupropion. Among unselected stimulant abusers these antidepressants may be quite limited, but when depressive symptoms are reduced, cocaine abstinence also appears to follow. Cerebral blood flow (CBF) defects also appear to be relatively common among stimulant abusers and to correlate with neuropsychological deficits. These CBF defects in cocaine abusers may respond to antistroke medications, and this potential for remediation builds on a rapidly evolving field of stroke pharmacotherapy. Finally, vaccines are under development that may reduce cocaine's rewarding effects and prevent relapse among abstinent formerly dependent patients.

Methods for screening medications as potential pharmacotherapies have used human laboratory studies employing cocaine administration as a surrogate efficacy assessment. Although this method needs validation with a gold standard of medications that have demonstrated efficacy in outpatient randomized clinical trials, these laboratory settings have been helpful in assessing medical safety during cocaine interactions. Neuroimaging of cerebral blood flow and of

"receptor" binding also holds promise for medication development.

With all of these pharmacotherapies the behavioral platform for their delivery is critical in retaining the patient in treatment and maintaining compliance with the medications. As a behavioral disorder, stimulant dependence is quite responsive to contingency management using a variety of reinforcers and schedules of reinforcement. Vouchers to purchase prosocial goods and services are the most common reinforcer used to initiate and maintain stimulant-free urines (95,97). Reinforcement schedules are typically on a one-to-one fixed ratio initially, with a progressive increase in the ratio of reinforcement and escalation in reinforcers as longer periods of abstinence are attained. The major problem with this approach has been maintaining abstinence after the reinforcers are withdrawn completely and developing a mechanism to obtain these types of reinforcers outside of a research setting. A more typical time limited therapy for clinical programs is cognitive behavioral therapy. Cognitive behavioral therapies have been examined in conjunction with pharmacotherapy, particularly using antidepressants, and have shown interesting additive effects (32). For example, at 1-year follow-up after a 3-month treatment period, those patients who got both the pharmacotherapy and the cognitive therapy showed more sustained abstinence than those who got either therapy alone. The behavioral treatments may also be most useful for abstinence initiation, particularly the contingency management and cognitive behavioral therapy approaches (32). Overall, the long-term outcome at 1 year is substantially enhanced by the use of psychotherapy in combination with medications.

ACKNOWLEDGMENTS

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