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Psychostimulant Abuse: The Case for Combined Behavioral and Pharmacological Treatments

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STITZER, M. L. AND S. L. WALSH. *Psychostimulant abuse: The case for combined behavioral and pharmacological treatments.* PHARMACOL BIOCHEM BEHAV **57**(3) 457–470, 1997.—Behavioral and pharmacological therapies have been used alone and in combination for the treatment of substance abuse; however, to date, no single treatment approach for psychostimulant abuse has demonstrated widespread efficacy. This paper describes the various functions that are served by both behavioral therapies and pharmacotherapies and their respective mechanisms of action. It is argued that combined treatments can be expected to produce additive effects because the two approaches operate through different and potentially complementary mechanisms. Illustrations of these underlying principles and experimental support for the use of combined treatments are drawn from smoking cessation research, which has broadly applied combined behavioral and pharmacological therapies for treating abuse of nicotine, a mild stimulant. In addition, the results of recent studies that have evaluated the efficacy of behavioral techniques and/or potential pharmacotherapies for treating cocaine abuse are reviewed. Finally, methodological strategies are recommended for future evaluations of combined therapy approaches to conclusively evaluate separate and combined efficacy of treatments for psychostimulant abuse. © 1997 Elsevier Science Inc.

Behavioral treatment Cocaine Drug abuse Combined treatment Community reinforcement Medications development Nicotine Pharmacological treatment Relapse prevention Smoking cessation Stimulants Treatment

THE conceptual and empirical basis for combined behavioral and pharmacological approaches to the treatment of stimulant abuse will be described in this paper. The first section examines the methods employed and functions served by behavioral versus pharmacological treatments. We propose the thesis that combined treatments can be expected to produce additive effects because the two approaches operate through different and potentially complementary mechanisms. The second section uses smoking cessation treatment to illustrate the separate and combined effects of behavioral and pharmacological therapies in the treatment of a prototypic stimulant abuse disorder. The data demonstrate that each type of treatment has only partial efficacy when implemented separately but that efficacy is enhanced when the two approaches are combined. The third and final section reviews the current state of the art for treatment of cocaine dependence and makes suggestions for the most rational approach to this treatment development effort. We conclude that evaluation of new medications for stimulant abuse needs to proceed with increased attention to the types of concurrent behavior therapy employed and to outcome measurement strategies that may enhance ability to detect alterations in drug use as well as complete abstinence. The reader is referred to a recent NIDA Monograph (69) for additional perspectives on the issues and data reviewed herein.

CONCEPTUAL FRAMEWORK FOR COMBINED THERAPIES

The primary goal of substance abuse treatment is to stop use of the target substance and then to support abstinence for as long as possible. Available to accomplish this mission are pharmacotherapies that involve administration of medications and behavioral or psychological therapies that involve interpersonal contact with a trained therapist. In this section we describe briefly the conceptual underpinnings, methods, goals, and mechanisms of each of these approaches and develop the thesis that the behavioral and pharmacological treatments operate by sufficiently different methods and mechanisms that their effects can be expected to be complementary and potentially additive when used in combination.

Pharmacotherapies

Pharmacological treatments for substance abuse grow out of a medical model that seeks to understand the disorder, and

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indeed all aberrant human behaviors, in terms of underlying neurochemical perturbations and imbalances. In the case of substance abuse, the neurochemical abnormality could be a preexisting perturbation that acts as a precursor to substance abuse and once corrected would eliminate the aberrant behavior (e.g., correcting an underlying depression). Alternatively, the imbalance or abnormality could be something caused directly by chronic exposure to drugs of abuse, in which case a medication might help to restore the organism to homeostasis more quickly. Thus, medications may relieve unpleasant physical withdrawal symptoms that frequently occur after discontinuing drug use. Once an organism has been exposed to reinforcing properties of a drug, it appears that the learning circuits activated are long-lived and difficult to eradicate (79). The effects of learning and conditioning during drug exposure may underlie drug craving, which is characterized by intrusive thoughts about the drug that persist well beyond cessation of use. Medications that could relieve craving would be particularly useful in the treatment of psychostimulant abuse. Finally, medications might have practical utility by functionally altering the biological effects of abused substances (i.e., alteration or blockade of drug effects). A medication that completely blocked, or at least markedly attenuated, the reinforcing effects of the abused drug could be an ideal treatment agent because elimination of the discriminative and reinforcing drug effects should concurrently result in reduction of drug-seeking and self-administration behaviors (62,63).

Currently, there are only three types of pharmacotherapies available for treatment of substance abuse. These are: a) agonists, such as methadone or the nicotine patch, that mimic the pharmacology of the abused drug and substitute for it, providing withdrawal relief and attenuating direct effects via cross-tolerance to the drug of abuse; b) antagonists, such as naltrexone, that can block the receptor and eliminate the pharmacological effects of the abused drug; and c) metabolic modulators, such as disulfiram, that alter the psychoactive effects of the abused drug by blocking its metabolism and/or causing accumulation of a toxic metabolite. Because these are the only types of medications currently known to be effective, they serve as the models for the development of medications to be used in the treatment of stimulant (i.e., amphetamine and cocaine) abuse. Medications with novel mechanisms of action may, of course, emerge through future development efforts.

Behavioral and Psychological Therapies

The development of specific pharmacotherapeutic interventions that can modulate effects of cocaine and other stimulant drugs and/or reverse the sequelae of chronic drug exposure could be extremely helpful for treatment efforts. However, experience to date suggests that no medication is likely to be a magic bullet that can operate independently to cure stimulant abuse. Thus, it is a virtual certainty that behavior therapies will be needed to act in concert with medications and to fulfill functions that cannot be addressed by medications alone.

In contrast to the medical model represented by pharmacological treatments, behavioral therapies or psychotherapies based on learning and psychosocial models of drug abuse propose that the dysfunctional behavior is developed and supported through mechanisms that include expectancies, modeling, and secondary social reinforcement as well as the primary direct reinforcing properties of abused drugs. Instead of targeting specific neurochemical systems or metabolic pathways, behavioral therapies and psychotherapies seek to directly alter drug-seeking and other behaviors of the drug abuser. Thus, any resultant effects on structure or function of the central nervous system are indirect. The goals of therapy are to stop drug use, to prolong periods of abstinence (achieving permanent abstinence if possible), and to enhance medication compliance as needed. Some of the most pharmacologically efficacious treatment medications available—the opiate antagonist naltrexone is an example—are essentially useless in practice because compliance is typically very poor in populations of opiate drug abusers (66,77). Techniques used to accomplish the first two goals include teaching skills to avoid relapse and improving the skills and resources available to sustain a nondrug-abusing lifestyle. It should be noted that substance abuse is one of the only chronic relapsing disorders where there is an expectation that one course of therapy will prevent relapse indefinitely. This may be an unrealistic expectation for a chronic relapsing disorder, and long-term care with repeated interventions may be needed to address substance abuse disorders fully. However, to the extent that the therapy enhances behaviors that are incompatible with drug use (e.g., correcting chronically dysfunctional employment and relationship problems), the long-term efficacy of therapy may be improved.

Three broad types or schools of therapy are generally used for individual treatment of substance abuse (family therapy and therapeutic community milieu treatments are also employed at institutions where expertise and resources are available): a) 12-step recovery, which seeks to fundamentally change the behaviors, beliefs, and values of the drug abuser via spiritual awakening and participation in a structured lifelong program of recovery (31,64); b) behavioral and cognitive–behavioral therapies (including relapse prevention skills training and community reinforcement therapy), which seek to equip the drug abuser with skills needed to resist drug use and to modify the environment such that nondrug sources of reinforcement are enhanced (87); and c) psychotherapies [such as supportive–expressive therapy (95)], which focus on feelings, perceptions, and interpersonal relationships of the drug abuser and seek to steer these into more satisfying and healthy directions so that the need to use drugs as a coping behavior is reduced. While this does not represent an exhaustive list of therapeutic approaches used in the treatment of substance abuse, it does include the most widely used approaches. In contrast to pharmacotherapies, where the goal is a highly specific intervention that targets the effects of a single drug or class of drugs, behavior therapies are thought to be generic and applicable across all categories of substance abuse. Thus, treatments developed for use with other types of substance abuse may also be effective for treatment of stimulant abusers.

Rationale for Combined Treatments

Although behavioral and pharmacological treatments are vastly different in their methods, they can be conceptualized as serving common treatment goals such as removal of drug-related cues that may promote relapse [see (52) for a more thorough analysis of functional similarities]. Further, it is possible that these two treatment approaches ultimately operate on a final common neurochemical pathway to produce beneficial effects. In spite of the potential overlaps in function and final common pathway, it seems clear that medications and behavior therapies operate by very different mechanisms to achieve improvements in drug-using behaviors. In the case of pharmacotherapies, activity is directed at modifying drug effects via alteration in neurochemical systems, whereas behavior therapies act directly to alter drug-seeking, with any effects on neurochemical systems being secondary. Thus, the

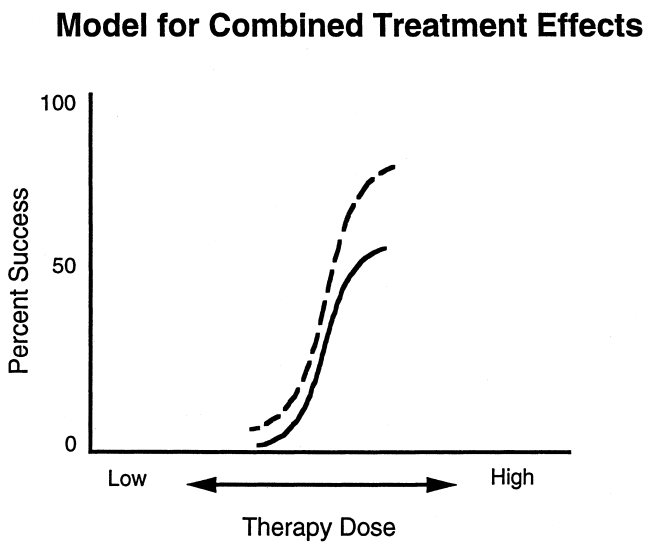

FIG. 1. A hypothetical model for combined effects of behavioral and pharmacological treatments. Percentage of successful cases is shown as a function of the dose of therapy delivered. A behavior therapy delivered alone (solid line) produces more successful cases as the dose (e.g., number and duration of sessions) is increased. However, the therapy has limited efficacy, with a ceiling at higher doses. When the behavior therapy is combined with a pharmacotherapy (dotted line), the maximum effect is increased. It is proposed that the boost in efficacy with combined treatment is due to additive effects of treatments with independent mechanisms of action.

main rationale for combining these treatments is that additive effects may be expected when drug-using behaviors are attacked using multiple interventions that operate via different mechanisms [see (10,42,43) for further discussion of the mechanism of combined behavioral and pharmacological therapies in treatment of substance abuse]. An important principle is illustrated for a hypothetical case in Fig. 1: currently available therapies, both pharmacological and behavioral, are only partially effective. However, when the two types of treatment are combined, an increase in maximum efficacy is observed. This principle will be illustrated in the next section for the case of tobacco dependence treatment and can be expected to operate in the treatment of cocaine and other stimulant abuse as well.

SMOKING CESSATION TREATMENT: A MODEL FOR COMBINED INTERVENTION

Smoking cessation provides a relevant and instructive example of the use of combined therapies and has been selected to illustrate the effects of combined treatment for three reasons. First, nicotine, which causes release of catecholamines from the adrenal medulla, has dominant actions in humans as a mild stimulant (7). Thus, principles that apply to its treatment may have relevance to treatment of other stimulant drugs as well. Second, effective pharmacotherapies are now marketed for the treatment of tobacco dependence in the form of the nicotine patch and nicotine gum. Finally, a considerable amount of research has focused on the interaction between pharmacological and behavioral therapies in the treatment of tobacco smoking and a rich data base is available.

Nicotine Pharmacotherapy

In a previous section, three desirable functions of pharmacotherapy were described: a) correction of underlying neurochemical imbalances that may cause or contribute to substance abuse, b) alleviation of postcessation withdrawal symptoms, including the persistent cognitive symptom of drug craving, and c) blockade or attenuation of reinforcing drug effects, with resulting reduction in self-administration of the abused substance. This section examines the effects of nicotine substitution therapy with regard to functions b and c, which are the relevant mechanisms of action for this therapy.

Tobacco withdrawal symptom relief. Cessation of tobacco use results in a reliable cluster of symptoms including irritability, anxiety, and difficulty concentrating (44,45), as well as objective performance disruption (84). Numerous studies have documented the ability of nicotine substitution therapies, including the patch (90) and gum (32,44,46), to at least partially relieve these symptoms. Figure 2 shows data from a study by Gross and Stitzer (32) in which subjects, randomly assigned to use placebo or active 2-mg nicotine polacrilex gum, rated symptoms weekly during a 10-week period of verified abstinence. The study showed that symptoms peaked during the first postcessation week for placebo gum subjects and then declined steadily over the first 4–5 postcessation weeks. Active gum subjects experienced fewer and milder symptoms from the start, and these symptoms were more quickly resolved. Specific symptoms reliably suppressed by nicotine substitution therapy included irritability, anxiety, difficulty concentrating, and increased hunger. The symptom of craving is also typically reduced by active as compared with placebo nicotine replacement therapy. For example, the right-hand panel of Fig. 2 shows unpublished data from the Gross and Stitzer (32) study illustrating the effects of 2-mg nicotine gum on weekly reports of craving. The small and statistically nonsignificant reduction of craving observed is consistent with other reports [e.g., (46)]. In some studies, however, craving reductions of similarly small magnitude produced by the nicotine patch or nicotine gum have achieved statistical significance [e.g., (44,90)]. These differences across studies may be accounted for, in part, by differences in sample size and resultant power to detect small effects. Thus, although nicotine substitution therapy attenuates craving to some degree, it clearly does not eliminate this troublesome symptom.

Attenuation of reinforcing drug effects. The effects of nicotine substitution on the reinforcing effects of cigarette smoking have been examined in several studies using subjective effect measures. These studies have directly or retrospectively assessed the subjective response to cigarettes in patients who are receiving various forms of nicotine replacement therapy. In one study (23), smokers wore active (delivering 15 mg nicotine/16 h) and placebo patches for 1 week each in counterbalanced order. During this time, they were instructed to smoke as usual in their natural environment and to visit the laboratory for data collection once weekly. Figure 3 shows subject ratings of the satisfaction derived from cigarettes during the previous week (satisfaction being a measure that is assumed to reflect the reinforcing properties of nicotine). These ratings were significantly reduced during active versus placebo patch treatment. However, the absolute magnitude of the reductions was in fact quite small. Mixed results have been obtained in other studies. Smoking satisfaction scores were reduced when subjects chewed active versus placebo nicotine polacrilex gum during a laboratory experiment (67), but were not altered in a dose–effect study of the nicotine patch (71).

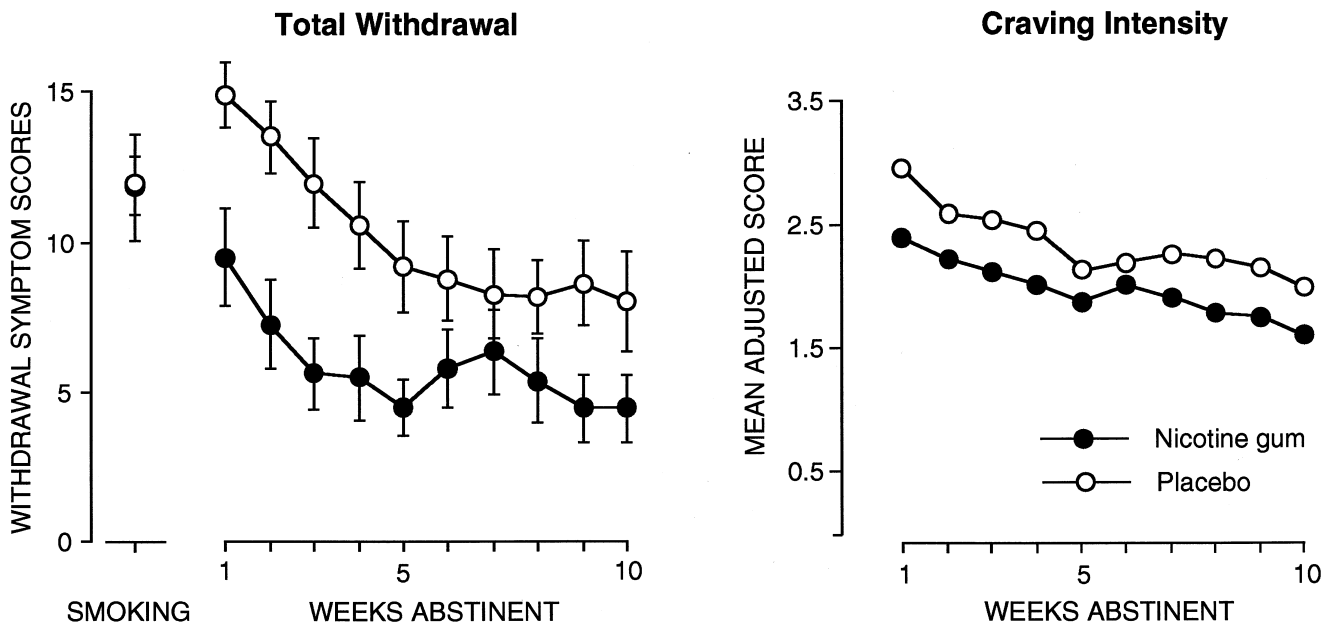

FIG. 2. Nicotine gum therapy for smoking cessation. The left-hand panel illustrates total scores on a 16-item tobacco withdrawal scale (mean ± SEM) for subjects using active 2-mg (closed circles) or placebo (open circles) nicotine gum during a 10-week treatment program. Data shown are means for 20 subjects per group who sustained abstinence for 10 postcessation weeks, with abstinence verified via frequent carbon monoxide checks (abstinence criteria = CO ⩽ 8 ppm). Each item was rated weekly by the patient during a clinic visit on a 4-point scale with 0 = none, 1 = slight, 2 = moderate, 3 = severe. The right-hand panel shows adjusted means from the single item "How strong are your cravings for a cigarette?"; baseline scores on this item were used as the covariate. This item is included in the total score shown in the left-hand panel. [From Gross and Stitzer (32).]

Thus, nicotine substitution, when used in therapeutically recommended doses, only partially and inconsistently attenuates the subjective effects of tobacco smoking.

Several studies have directly examined the reinforcing effects of tobacco as a function of nicotine substitution levels using the self-administration paradigm (i.e., the number of cigarettes smoked). Nemeth-Coslett and colleagues (67) found that subjects smoked an average of 2.64 cigarettes in a 90-min laboratory session when they had chewed gum containing 8 mg nicotine, as compared with 3.04 cigarettes when placebo gum had been chewed prior to the session. In a study by Pickworth et al. (71), where subjects could smoke ad lib while wearing transdermal patches containing 0, 22, or 44 mg nicotine, smoking decreased from 17 cigarettes per day for the placebo patch condition to 13.4 cigarettes per day for the highest dose patch condition. Finally, Benowitz and Jacob (8) conducted an elegant study in which placebo or active nicotine was infused intravenously over a 14-h period to subjects residing on a residential research unit under close medical supervision. Nicotine infusion doses were designed to match the subjects' plasma nicotine levels observed during normal smoking and thus to simulate a nicotine level higher than that typically achieved by currently available nicotine substitution products. The average number of cigarettes smoked decreased from 25.5 on placebo infusion days to 19.9 on nicotine infusion days, a reduction of 4.5 cigarettes per day or about 20%. Thus, data from cigarette self-administration studies support the conclusions from studies incorporating subjective effects ratings: nicotine substitution is only partially effective in blocking the reinforcing effects of tobacco cigarette smoking.

Overall, nicotine substitution therapy appears to be most effective in relieving somatic and psychological symptoms of tobacco withdrawal (irritability, anxiety, difficulty concentrating, increased hunger), but at doses typically employed has only partial efficacy in attenuating the reinforcing effects of tobacco smoking, in reducing tobacco self-administration, and in relieving postcessation cravings. Thus, nicotine substitution therapy serves some but not all of the functions that are desirable for a pharmacological intervention.

Smoking Cessation Behavior Therapy

Among the several distinct types of behavioral and psychological therapy described above for treatment of substance abuse disorders, a cognitive–behavioral relapse prevention skills training approach has been widely adopted for use in smoking cessation treatment. This involves teaching smokers to identify and avoid high-risk relapse situations and to adopt alternative coping behaviors that can be used instead of smoking when risky situations cannot be avoided. Although the elements of treatment may be similar, there are wide variations in the amount and intensity of therapy provided across treatment settings. For example, while relapse prevention strategies are described in all smoking cessation self-help pamphlets and booklets, more intensive implementation during face-to-face counseling includes individualized identification of high-risk situations and supervised skills practice. This consistency in content but variation in intensity of therapy allows dose–effect relationships to be examined for behavioral as well as pharmacological treatments.

In a previous section, three desirable functions of a behavioral therapy were outlined. These were: a) stop drug use (i.e., initiate abstinence), b) prolong abstinence, usually by teaching relapse prevention skills and enhancing behaviors incom-

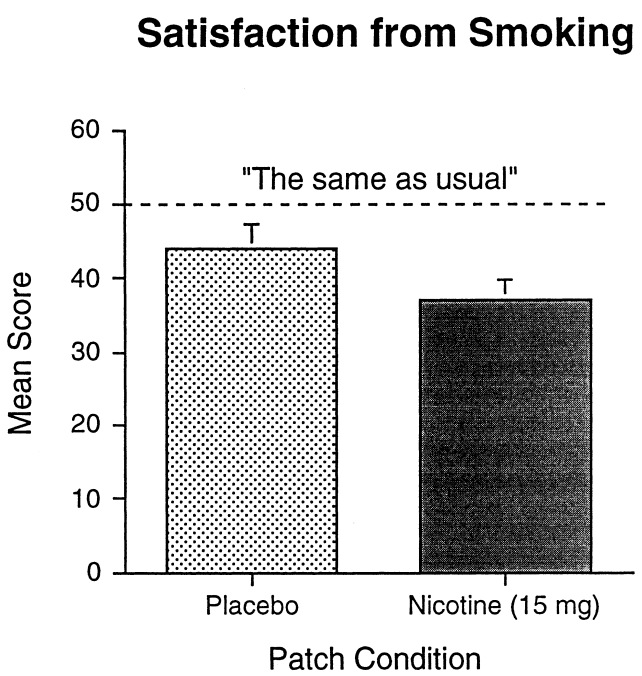

FIG. 3. Subjective effects of cigarette smoking during placebo versus active (15 mg/24 h) nicotine patch treatment. Subjects rated satisfaction from smoking during laboratory visits conducted on the last day of a 7-day period of patch treatment; ratings were retrospective for the previous week, and active versus placebo patch treatment order was counterbalanced. Subjects rated satisfaction from smoking on a 10-cm visual analog scale with one end indicating "more than usual," the other end "less than usual," and the middle "exactly the same as usual." Data shown are means ± 95% confidence intervals for 30 subjects. Reduced satisfaction from smoking was statistically significant ($p < 0.05$). [From Foulds et al. (23).]

patible with drug use, and c) improve medication compliance. Only abstinence prolongation via relapse prevention training will be discussed in detail here.

Abstinence initiation and medication compliance. With regard to abstinence initiation, clinical trials of smoking cessation interventions rarely report these rates both because smokers who volunteer for behavioral treatment tend to have high abstinence initiation rates and because the emphasis of these clinical trials is generally on long-term outcomes. Thus, the first relapse survival point reported may be at 4–6 weeks postcessation, a point that includes both those patients who never quit and those with early relapse. Because reliable abstinence initiation is an important goal of an efficacious treatment, it would be helpful if this outcome was more uniformly reported in clinical trials involving behavioral interventions. Medication compliance is a more significant problem with nicotine gum than with the patch. Although compliance with relatively higher rates of gum use has been associated with better treatment outcomes [e.g., (51)], the impact of participation in behavior therapy on gum use compliance has been infrequently evaluated or reported (42,43).

Abstinence prolongation. There has been considerable interest in evaluating the specific efficacy of the relapse prevention skills training element of smoking cessation therapy, as this has both conceptual and practical importance in developing cost-effective treatment interventions for smokers. Three well-designed studies have demonstrated the partial efficacy of relapse prevention skills training (29,36,85). All of these studies were characterized by rigorous experimental design, including random assignment to treatment conditions and biochemical verification of abstinence outcomes. All studies delivered intensive (6–10 h) relapse prevention training whose effects were contrasted with an intensity-matched control condition. Thus, experimental and control subjects met with counselors for an equal amount of time, but control subjects engaged in discussions of motivational and health-related issues, whereas only the experimental groups received explicit relapse prevention skills training. Remarkable consistency was obtained in the outcomes across these studies. One-year verified abstinence rates in the Hall et al. study (36) were 45.5% for skills training versus 30% for discussion control subjects. In the Stevens and Hollis study (85), confirmed 1-year abstinence rates were 41% for skills training and 34% for discussion control subjects. In the Goldstein et al. (29) study, where only 6-month outcomes were reported, the behavioral treatment group attained 36.7% abstinence compared with 17.5% for an educational control group. Figure 4 shows results from the two studies reporting 1-year outcomes (36,85), illustrating the small but consistent improvement in success rates engendered by relapse prevention skills training. It is also notable from examination of the figure, however, that the teaching of these skills did not slow or prevent relapse from occurring over time. Thus, the small magnitude of effect and the failure to slow relapse over time leads to the conclusion that skills training has only partial efficacy in smoking cessation treatment.

Interaction of Behavioral and Pharmacological Therapies

This section demonstrates that the combination of two partially effective therapies that operate via different mechanisms can enhance success rates beyond those typically observed when either treatment is delivered alone. Evidence for this assertion comes primarily from across-study comparison of smoking cessation trials that employed different intensities of behavior therapy while evaluating the efficacy of nicotine polacrilex gum (16) or the nicotine patch (21). In general, these across-study comparisons have documented higher overall success rates in clinical trials employing more versus less intensive behavior therapy interventions. For example, in studies employing the nicotine patch, absolute success rates at the end of treatment are typically twice as high when intensive face-to-face therapy as compared with minimal intervention behavior therapy (e.g., physician advice) is delivered (20).

An illustration of this principle is provided by one recently published report of two sequential nicotine patch studies conducted at the same treatment site (20) in which active versus placebo transdermal patches were tested under two different behavior therapy support conditions. In the first study, subjects received 1-h therapy sessions each week for 8 postcessation weeks, whereas in the second study, sessions were only 10–20 min in duration and were designed to simulate the type of adjuvant treatment a smoker could receive in a physician's office. Figure 5 shows end-of-treatment outcomes (6 or 8 weeks postcessation for the second and first studies, respectively) as a function of treatment intervention. First, it is clear that active patch enhanced abstinence rates under both behavior therapy intervention conditions. Second, it can be seen that high-intensity behavior therapy produced better absolute rates of abstinence than did low-intensity therapy. Third, it is interesting to note that active patch and high-intensity behavior therapy produced very similar outcomes when delivered

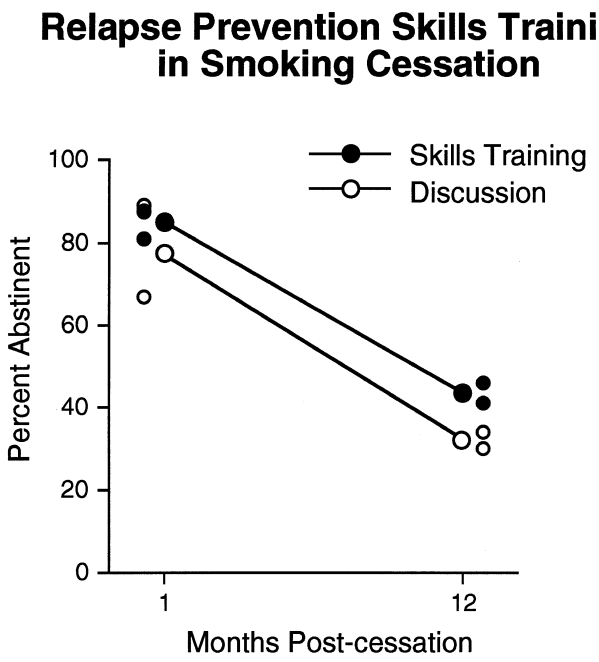

FIG. 4. Summary of two studies of cognitive–behavioral relapse prevention treatment for smokers. The percentage of subjects abstinent at the end of treatment and at 12-month follow-up is shown for each study separately with smaller symbols; means for the two studies are shown in larger symbols and connected by lines. In both studies, smoking cessation treatment patients were randomly assigned to receive relapse prevention skills training (closed circles) or an intensity-matched discussion control therapy (open circles). In a study by Hall et al. (36), subjects were assigned at treatment entry to relapse prevention (n = 57) or discussion therapy (n = 66); treatment was delivered in six sessions during treatment weeks 1, 2, 3 (two sessions), 4, and 6. All subjects also received rapid or paced smoking exercises during the first 3 postcessation weeks; data have been collapsed on this factor. Relapse prevention skills training included coping skills rehearsal, muscle relaxation techniques, and commitment enhancement exercises. Discussion control utilized a questionnaire on smoking attitudes to generate discussion and omitted any specific skills training interventions. In a study by Stevens and Hollis (85), all subjects received an intensive 4-day smoking cessation program with daily (Monday through Thursday) 2-h group meetings. Following this, abstinent subjects were randomly assigned to: a) skills conditions in which they developed and actively rehearsed coping strategies during three weekly meetings (n = 184), b) social support control condition in which they discussed, but did not develop or rehearse, specific coping strategies during three weekly meetings (n = 205), or c) no-treatment control condition, without additional meetings scheduled (n = 198). Data are shown for groups a and b; the 12-month outcome for group c did not differ from that for group b.

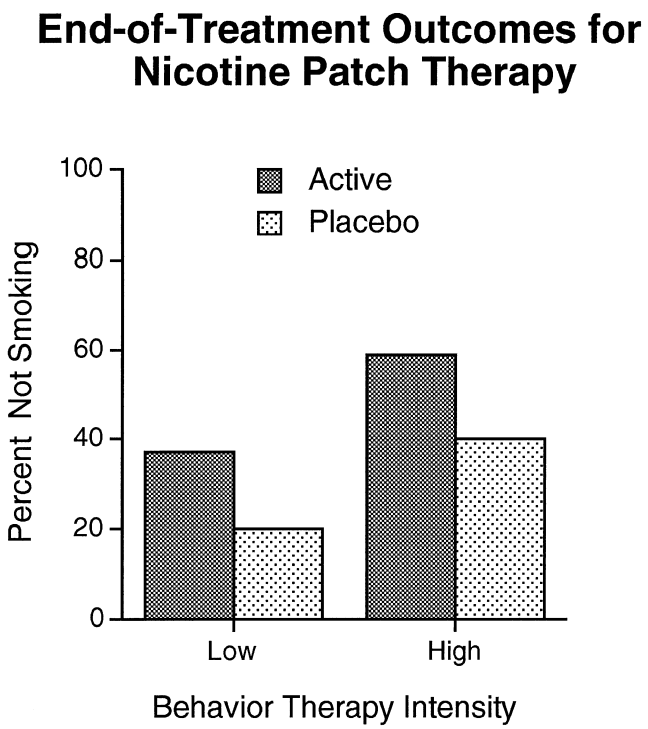

FIG. 5. End-of-treatment outcomes are shown for two studies of the clinical effectiveness of the nicotine patch that utilized different counseling procedures. In the first study, subjects randomly assigned to receive active patch (n = 44) were given 8 weeks of high-dose (22 mg) patch therapy; placebo subjects (n = 43) also received 8 weeks of patch. All subjects received weekly group counseling sessions of approximately 1 h duration. In the second study, subjects randomly assigned to receive active patch (n = 57) received 4 weeks of high-dose (22 mg) patch therapy followed by 2 weeks of tapered dose (11 mg); placebo subjects (n = 55) received 6 weeks of patch. Counseling consisted of eight 10–20-min individual weekly sessions. In both studies, therapy was conducted by clinical psychologists or advanced psychology graduate students. End-of-treatment data reported are from postcessation weeks 8 and 6 for the first and second studies, respectively. [From Fiore et al. (20).]

alone. Finally, it can be seen that the best outcomes—nearly 60% abstinent at the end of treatment—were achieved when active patch was combined with high-intensity behavior therapy. Similar end-of-treatment abstinence rates were more recently reported by Jorenby and colleagues (48) for smokers treated with active patch under two similar intensities of behavior therapy.

Smoking Cessation Treatment Summary

Previous sections of this paper have discussed the effects of both pharmacological and behavioral therapies for smoking cessation. Each type of intervention serves important functions and can be shown to improve smoking cessation outcomes compared with relevant controls. However, the data also demonstrate that neither existing behavioral nor pharmacological therapies are fully effective in accomplishing their goals. Medications do not fully block reinforcing drug effects nor completely suppress abstinence symptoms and cravings; behavioral therapies do not fully prevent relapse in spite of their best efforts to teach relapse prevention skills. Data presented in the last section, however, also support the conclusion that a combination of pharmacological and behavioral therapies, each of which are only partially effective, can boost end-of-treatment success rates beyond those expected when either treatment is delivered alone. This finding is not a foregone conclusion. It is possible instead that the combination of therapies would simply reproduce effects expected from the most effective component of the combination. Typically, in stop smoking clinical trials, differential outcomes observed at the end of treatment are still apparent at longer term evaluation time points. However, additional relapse also invariably occurs after treatment ends, and differences between treatment groups can disappear over time [e.g., (48)]. This high-

lights the need for interventions that can more reliably slow or prevent long-term relapse in addition to those interventions already available that can produce high initial success rates.

PSYCHOSTIMULANT TREATMENT: STATE OF THE ART

Smoking cessation treatment research provides an excellent model for proceeding with the evaluation of treatments for cocaine abuse. This model suggests that it is important to test the elements of each treatment for functional utility, to vary the dose of both pharmacological and behavioral treatment elements when testing efficacy in clinical populations, and to explicitly conduct interaction studies. In this section, we review the current status of treatments for cocaine abuse, addressing both medications and behavioral therapies. Finally, some strategies will be suggested for continued treatment development efforts.

Medications Development: The Search for a Cocaine Pharmacotherapy

As previously noted, the existing models for medications development efforts include agonists that activate the same receptors targeted by drugs of abuse, antagonists that block receptors, and metabolic modulators that convert the drug of abuse into an inactive or toxic by-product. In considering strategies for the development of psychostimulant treatment medications, it is important to recognize that these drugs of abuse, including cocaine and amphetamine, typically produce their pharmacological actions via complex effects on several distinct neurochemical systems. Because the goal is to achieve a highly specific interaction between the medication and the effects of the abused drug, medications development efforts are primarily targeting the stimulant-related neurochemical systems, including the dopaminergic, serotonergic, and noradrenergic systems (78). A vigorous medications development effort is currently under way that has focused on identifying, developing, and testing pharmacological agents for the treatment of cocaine abuse, dependence, and withdrawal. The clinical evaluation of potential pharmacotherapies most frequently has been stimulated by promising preclinical findings from neurochemical and behavioral studies demonstrating some pharmacological interaction with cocaine. Clinical evaluations for efficacy against cocaine abuse have been conducted in the laboratory and in clinical settings using either open-label or double-blind designs. Perhaps most impressive in this endeavor is the sheer number of medications that have been screened for their ability to alter the effects of cocaine and the broad range of drug classes represented in this listing (53). Because of the tremendous number of approved and investigational drugs that have been screened, this discussion will be limited to those medications that have progressed beyond preclinical screening to evaluation in human laboratory and/or clinical trials.

Many of the compounds that have been screened for efficacy can be grouped into categories based on mechanism of action and were initially identified, in many cases, as potential therapeutics because they act upon a neural substrate shared with cocaine. Preclinical studies have extensively documented the role of the central mesolimbic dopamine system in mediating some of the reinforcing effects of cocaine [see (59,94) for review], and for this reason, many drugs whose actions are exerted through the dopamine system have been clinically evaluated. These include drugs that act either: a) directly or indirectly as dopamine agonists, such as bromocriptine (60,75), mazindol (9,61,74,86), amantadine (1,28,38,88), methylphenidate (50), L-dopa and carbidopa (80), oral cocaine (33), and selegiline (34), or b) as dopamine antagonists, including haloperidol (81,82) and flupenthixol (25). A second class of drugs that has been evaluated extensively in humans is the antidepressant class that share cocaine's ability to inhibit neuronal reuptake of the monoamines, including desipramine (13,14,26,27) and fluoxetine (4,5,30,91). The third category of agents includes drugs whose actions are mediated through the central opioidergic systems, including buprenorphine (24,57,89), methadone (68,76), and naltrexone (56,57,92). Finally, carbamazepine, an anticonvulsant that was proposed as an anticraving medication (35), has been evaluated in a number of double-blind clinical trials (18,58,65). Although some other drugs have been proposed as potential treatments based on information obtained from case reports, including controversial agents such as ibogaine and the fenfluramine–phentermine combination, published reports from controlled evaluations of these compounds are not yet available.

In spite of the far-reaching effort to identify and screen potential therapeutic agents, no medication has been identified yet that has clear utility for the treatment of cocaine abuse. Although it is impossible to provide a comprehensive review of all the medications development efforts for cocaine treatment, it is valuable to review the results for a few therapies that have demonstrated some potential utility in controlled human laboratory evaluations. What has failed to materialize for these compounds is consistently supportive data from outpatient trials demonstrating clinical efficacy. In this section, we review select medications that fit this profile of screening outcomes.

Desipramine, a commonly used antidepressant that acts primarily as an inhibitor of norepinephrine reuptake, has probably been evaluated for efficacy against cocaine abuse in more laboratory studies and clinical trials than any other compound. An early open trial reported that desipramine maintenance produced decreases in cocaine craving and cocaine abuse (26). A subsequent randomized 6-week clinical trial demonstrated impressive efficacy for the medication, with 59% of desipramine-treated (2.5 mg/kg) patients showing at least 3–4 consecutive weeks of cocaine abstinence compared with 25% and 17% abstinent subjects in comparison medication and placebo control groups, respectively (27). Fischman and colleagues (22) followed up on these early reports and conducted the first human laboratory evaluation of desipramine in cocaine abusers. Using a placebo-controlled design, the pattern of cocaine self-administration and the subjective and physiological responses to intravenous cocaine were examined during maintenance on placebo and desipramine (the average desipramine dose was $\sim$175 mg/day and was based on plasma concentration). Desipramine did not alter cocaine self-administration; however, it did significantly alter some subjective measures of cocaine's effects in comparison to placebo. Specifically, desipramine significantly decreased scores on a visual analog measure of "I want cocaine" following administration of both active and placebo cocaine (Fig. 6). In addition, desipramine potentiated the elevation of heart rate and blood pressure produced by cocaine alone.

In a second cocaine challenge study, Kosten and colleagues (55) evaluated the physiological and subjective effects of intravenous cocaine in outpatient volunteers during maintenance on placebo and desipramine (150 mg/day). Desipramine did not alter subjective responses to measures sensitive to the euphorigenic effects of cocaine (e.g., "high" and "rush"); however, subjects reported significantly lower ratings and shorter duration for "desire for cocaine" during maintenance on the

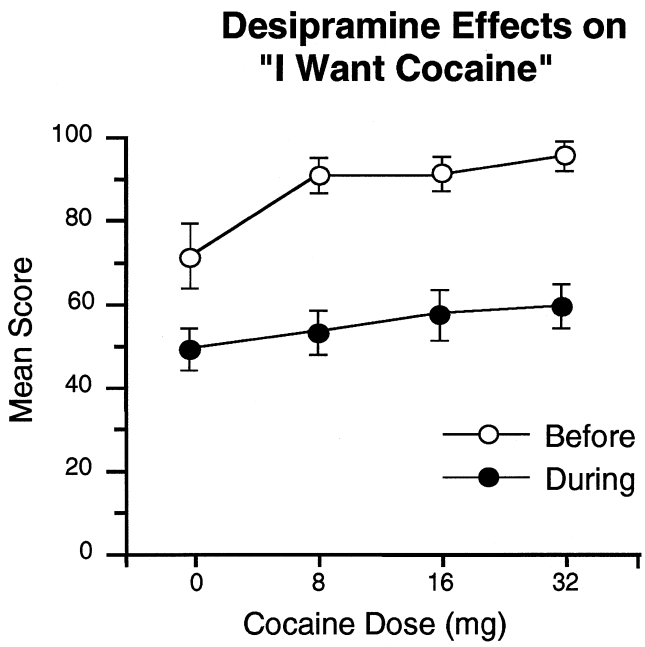

FIG. 6. Volunteers with a history of cocaine abuse and residing on an inpatient clinical research unit made a series of choices (up to seven per session) to receive intravenous doses of placebo versus cocaine (0, 8, 16, and 32 mg), with each cocaine dose (versus saline) tested during a separate independent session. Before and after receiving cocaine, subjects completed a battery of questions that included a rating on the statement "I want cocaine," which was rated along a 10-cm line labeled "not at all" on one end and "extremely" on the other. Data shown are postcocaine ratings averaged across choice trials for each subject. Data labeled "Before" were collected during the week prior to initiation of desipramine maintenance. Desipramine maintenance was initiated on an outpatient basis; doses were raised until blood levels of 80–150 ng/ml were achieved, and these levels were maintained for 3 weeks. During the third week of desipramine maintenance, subjects were readmitted as inpatients for a second series of cocaine choice determinations; data collected at this time are labeled "During." Data shown are means of 10 subjects ± SEM. [From Fischman et al. (22).]

active drug. These results are similar to those of Fischman and colleagues (22), and together, these studies suggest that desipramine treatment may decrease craving for cocaine ("desire" or "want") but does not produce a robust reduction in the euphorigenic or reinforcing properties of the drug. Kosten and colleagues (55) also observed that the pressor effects of cocaine were potentiated by desipramine, suggesting that this potential pharmacotherapy may actually increase the medical risk associated with cocaine use.

Double-blind trials evaluating the efficacy of desipramine for the treatment of cocaine abuse have since been conducted in patients who are: a) primary cocaine abusers (13,37), b) depressed cocaine abusers (96), and c) cocaine abusers who are methadone-maintained (2,11,54). Whereas many of these trials evaluated only the pharmacotherapeutic effects of desipramine compared with placebo, others systematically varied the level of a behavioral treatment as an additional factor (11,13,37).

Hall and associates (37) conducted a placebo-controlled evaluation of desipramine using a 2 × 2 balanced design that assessed the efficacy of the standard psychosocial treatment versus an enhanced treatment intervention. This study was conducted in two phases: a 2-week inpatient phase, where patients were inducted onto their study medication and received counseling, followed by an 8-week outpatient phase, during which patients reported to the clinic for medication. The primary difference between the standard treatment and the enhanced "continuity of care" treatment was that patients in the latter group had the same counselor during both the inpatient and outpatient phases and they joined outpatient therapy groups while still residing as inpatients. No beneficial effects of desipramine were observed for cocaine use or treatment attendance. However, the continuity of care treatment increased treatment attendance and increased early, but not later, cocaine abstinence.

A second placebo-controlled study also evaluated desipramine in combination with two different levels of behavioral treatment (13). Patients (n = 139) were assigned to receive either desipramine (average 200 mg/day, with final dose based on plasma concentration) or placebo, with half of the patients in each medication group receiving standard clinical management or an intensive relapse prevention therapy. After 6 weeks of treatment, desipramine was found to be more effective than placebo at reducing cocaine use; however, this was a transient effect and no significant effects of medication were observed on cocaine use or treatment retention by the end of study. Similarly, no robust between-group differences were found during treatment as a function of behavioral therapy assignment. In summary, data obtained from placebo-controlled trials of desipramine do not support the use of this drug as a treatment for cocaine abuse.

Fluoxetine is another antidepressant compound that has been evaluated in humans in both the laboratory and in several clinical trials. Fluoxetine acts as a selective serotonin reuptake inhibitor and produces far fewer side effects (including pressor effects) than the classical antidepressants such as desipramine (17,93). In a recent human laboratory study, volunteers with histories of cocaine abuse received intravenous cocaine challenges during maintenance on placebo and fluoxetine at doses up to 40 mg/day (91). Fluoxetine at 40 mg significantly reduced subjective ratings of cocaine effects on measures including "magnitude of drug effect," "liking for cocaine," and "rush" (Fig. 7). The observed attenuation of subjective effects was correlated with plasma concentrations of fluoxetine and its active metabolite, norfluoxetine, such that higher plasma fluoxetine levels led to lower ratings of cocaine's effects. Importantly, no adverse interactions were observed between cocaine and fluoxetine when given in various dose combinations. These data suggest that fluoxetine could attenuate some of the subjective effects of cocaine that may be related to its euphorigenic and reinforcing properties.

Open-label and double-blind studies have assessed the efficacy of fluoxetine in primary cocaine abusers (19,30) and in dually diagnosed cocaine/opiate abusers enrolled in methadone-maintenance treatment with or without concurrent depression (4,5,30,70,72). A preliminary open trial yielded promising results suggesting that fluoxetine was effective at reducing cocaine abuse (5). In this study, methadone-maintained cocaine abusers (n = 16) received fluoxetine at an average daily dose of 45 mg for 9 weeks and participated in once-weekly counseling. Self-reports of drug use and objective indices of cocaine use (i.e., quantitative analysis of benzoylecgonine) both showed significant declines over the course of treatment, indicating a beneficial effect of fluoxetine on cocaine abuse.

Despite these positive laboratory and open-label results, subsequent double-blind placebo-controlled trials have been

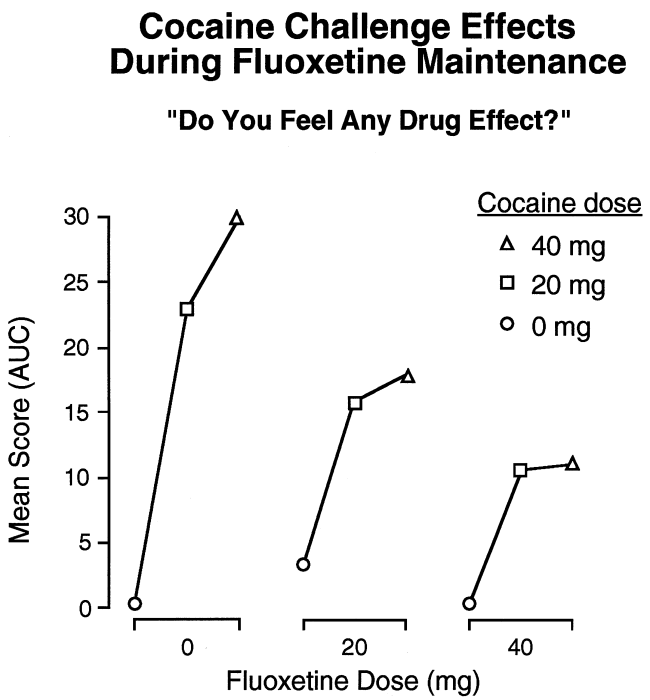

FIG. 7. Volunteers with a history of cocaine abuse and residing on an inpatient clinical research unit were maintained successively on 0, 10, 20, 30, 40, and 0 mg/day fluoxetine. Placebo doses were in effect for 1 week, whereas each active dose was in effect for 3–4 consecutive days. Cocaine challenge was conducted at each fluoxetine level after the third consecutive day at that dose. During cocaine challenge, subjects received three intravenous injections of 0, 20, and 40 mg cocaine given 90 min apart. Following each injection, subjects repeatedly answered a battery of questions that included the question "Have you felt any drug effect?" by positioning an arrow along a 100-point line on a computer screen marked with "none" at one end and "extremely" at the other. Area-Under-the-Curve (AUC) was calculated for each subject using data collected during the first 15 min postinfusion. Data shown are means for five subjects. [From Walsh et al. (91).]

largely negative, with few exceptions. One small pilot study conducted with primary cocaine abusers ($n = 45$) investigated the efficacy of fluoxetine at 0, 20, 40, and 60 mg/day for a 12-week period, with all patients receiving standard counseling twice weekly (19). Objective assessment of cocaine use (i.e., urinalysis) suggested that patients receiving 60 mg of fluoxetine used more cocaine than those patients assigned to placebo, whereas the other treatment groups did not differ. Significant improvement was observed over time for all groups for self-reported measures of cocaine use and various indices of craving (e.g., "want," "need"), but these were not systematically related to fluoxetine dose. The investigators attributed the observed improvement across groups to the efficacy of the psychotherapeutic intervention. However, this study had limited power to detect significant differences between the groups because of the small number of subjects initially enrolled (~10/group) and the high rate of patients dropping out of the study.

One of the largest clinical trials to date randomly assigned primary cocaine abusers ($n = 228$) to receive either 0, 20, or 40 mg fluoxetine/day for up to 12 weeks after stabilization (30). This study also evaluated the effect of varying the number of treatment visits such that, within each treatment group, half of the patients were assigned to five visits/week and the other half to two visits/week. Retention in the study was inversely related to fluoxetine dose, with patients receiving 40 mg dropping out earlier than those receiving 20 mg and patients receiving placebo staying in treatment the longest. Moreover, assignment to fewer mandatory clinic visits led to better retention across all dose assignments. These investigators also conducted a much smaller placebo-controlled trial in methadone-maintained cocaine abusers and found that fluoxetine at 20 mg did not significantly decrease cocaine use in comparison to placebo (30).

Batki and colleagues have also completed two double-blind trials of fluoxetine: one conducted in primary crack cocaine users and one in cocaine-abusing patients who were methadone-maintained. In the crack cocaine abusers, fluoxetine improved treatment retention in comparison to placebo but did not alter cocaine abuse (6). In methadone-maintained patients, fluoxetine treatment significantly decreased benzoylecgonine concentrations in comparison to placebo over the 12-week trial (4). Overall, these data suggest that fluoxetine may be ineffective in primary cocaine users but may be useful for treating patients with polysubstance abuse histories.

The study by Batki et al. (4) raises an important question regarding selection of outcome measures for clinical trials with cocaine pharmacotherapies, in particular the method and frequency of urinalysis testing. Qualitative testing is relatively insensitive to small to moderate changes in drug use and is most useful in detecting continuous abstinence, whereas quantitative testing provides a means of evaluating clinically meaningful improvement in drug abuse (73). Despite these limitations, qualitative testing is most widely used because it is more efficient and less costly than quantitative analyses. However, the relative insensitivity of qualitative urinalysis to changes in drug use could lead, under some circumstances, to discarding a potentially beneficial pharmacotherapy.

Behavior Therapy for Cocaine Abuse

In addition to the behavior therapy evaluations reviewed above that have been conducted as part of pharmacotherapy clinical trials, three distinct types of behavior therapy have been specifically evaluated for efficacy in cocaine abusers. Kang et al. (49) concluded that once per week interpersonal psychotherapy does not appear to be a particularly effective modality with cocaine abusers. This was based on observation of a 19% overall abstinence rate at 6–12 months posttreatment that was independent of the type of psychotherapy treatment (individual, family, or group) delivered. A cognitive–behavioral relapse prevention treatment has been developed that is similar to that described for smoking cessation but adapted to the needs of cocaine abusers (12). In one small ($n = 42$) study, 43% of patients treated with relapse prevention were abstinent at the end of a 12-week treatment compared with only 19% of comparison patients receiving psychotherapy (14). A second larger ($n = 97$) study by this group (13) found no during- or end-of-treatment differences in outcome for patients treated with relapse prevention skills training versus a clinical management comparison treatment; mean longest consecutive days of abstinence ranged from 18 to 24 days across treatment conditions. However, during the 12-month follow-up, a group difference began to emerge (15): subjects who had received relapse prevention skills training continued to decrease their cocaine use, as indicated by lower

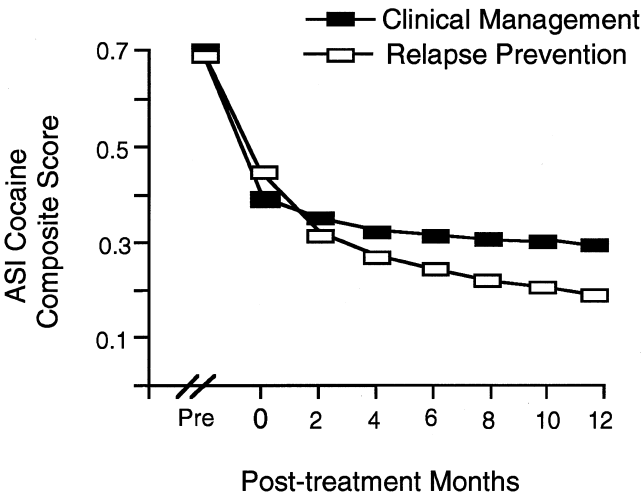

FIG. 8. Evaluation of relapse prevention skills training in cocaine abusers. Subjects were cocaine abusers who had been randomly assigned to receive 3 months of weekly individual relapse prevention skills training (follow-up sample $n = 52$) or a clinical management therapy with the same number of individual therapy sessions but no specific skills training interventions (follow-up sample $n = 45$). The original study included a desipramine versus placebo comparison as well in a 2×2 design; desipramine produced effects no different from placebo, and this treatment factor has been collapsed for presentation of behavior therapy results. The Addiction Severity Index (ASI) cocaine composite score was based on structured interviews conducted at 1, 3, 6, and 12 months after treatment termination by a rater blind to treatment conditions; the composite score includes frequency, intensity, and severity of problems associated with cocaine use. [From Carroll et al. (15).]

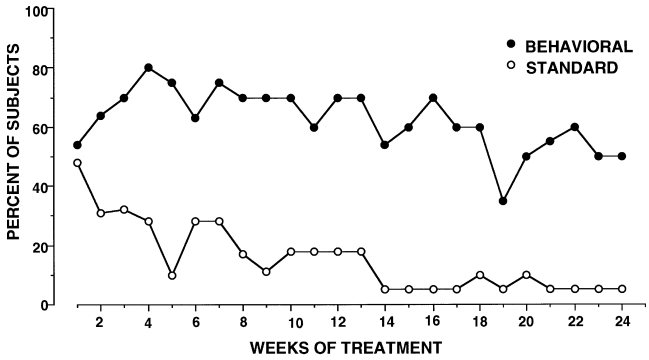

FIG. 9. Cocaine abstinence during evaluation of a 24-week behavioral treatment program. Subjects were cocaine abusers randomly assigned to receive behavioral ($n = 19$) or standard ($n = 19$) treatment. Counseling in the behavioral treatment group was based on the community reinforcement approach; sessions were offered twice weekly for the first 3 months and once weekly for the second 3 months. Treatment included reciprocal relationship counseling with a drug-free spouse, friend, or relative, relapse prevention skills training, employment and recreational counseling, and disulfiram therapy for those with alcohol problems (received by 42% of patients at some time during treatment). Standard therapy was based on the 12-step disease model of treatment; one group and one individual session was offered during the first 12 weeks, reduced to one group or one individual session during the second 12 weeks. Treatment included supportive and confrontative therapy and didactic lectures and videotapes on cocaine dependence, AIDS, the disease model of addiction, and the self-help orientation. A family member was invited to participate in therapy during week 9. Patients were expected to participate in self-help groups and to identify a sponsor by week 12. Patients in the behavioral, but not the standard, therapy also received cash-value vouchers for cocaine-free urines. These could be exchanged for goods and services in the community as deemed compatible with treatment goals. The value of vouchers escalated with successive cocaine-free urines and reset to an original low value if a positive urine was submitted. A continuously abstinent patient could receive $997.50 worth of retail goods during the first 12 weeks, after which each cocaine-free urine earned a $1.00 state lottery ticket. Patients in both groups received intensive (three times per week) urine testing at the behavioral therapy clinic; urine testing results were made available to behavioral but not standard care patients. Data shown are the percentage of patients with verified cocaine abstinence during successive treatment weeks. [From Higgins et al. (40).]

scores on the Addiction Severity Index, whereas this was not true for control subjects (Fig. 8). Thus, the limited data available on relapse prevention skills training for cocaine abusers suggest that this therapy has only partial efficacy in preventing relapse.

Consistent with the generic utility of behavioral treatments across specific types of substance abuse, a treatment originally developed for treatment of alcoholics called the community reinforcement approach (3,47) has recently been modified and adapted for use with cocaine abusers and has demonstrated promising efficacy (39–41). Community reinforcement treatment includes interventions to improve marital/family relations as well as vocational, social, and recreational activities. The common goal across these different treatment components is to enrich the quality of the cocaine user's life when abstinent. However, should drug use occur, procedures are arranged to produce a temporary time-out from the enriched environment. To supplement the skills training aspects of therapy, a token economy procedure has been added for use with cocaine abusers in which patients can earn cash-value vouchers exchangeable for retail items upon demonstrating recent abstinence from cocaine via urinalysis testing. To promote sustained abstinence, the value of the vouchers increases with each consecutive cocaine-negative specimen delivered during a 12-week period, and cocaine-positive specimens reset the value of vouchers back to their initial low level. Those who were continuously abstinent (all cocaine negative urine tests) could earn approximately $1000 worth of retail items during the 12-week program.

Two initial trials examined the efficacy of community reinforcement treatment compared with standard outpatient drug counseling based on the disease model of drug dependence and the 12 steps of recovery (40,41). Both treatments were delivered by experts in the respective approaches during once- or twice-weekly sessions. In both trials, the behavioral treatment retained patients significantly longer and produced significantly better outcomes on measures of drug use than did standard counseling: the percentage of patients abstinent at 12 weeks was approximately 70% in the behavioral treatment groups versus about 20% in the standard care comparison group (Fig. 9). Sustained periods of abstinence were also observed in individual subjects. For example, 68% of patients in

the behavioral group achieved 8 weeks of documented, continuous cocaine abstinence versus 11% of those in the counseling group. Silverman and colleagues have examined the voucher-incentive portion of this therapy with a treatment-resistant group of cocaine-abusing methadone patients (83). Among patients who could earn cash-valued vouchers for cocaine-free urines, approximately 50% were abstinent at the end of the 12-week trial as compared with 15% of control subjects, who received vouchers independent of behavior.

In summary, two types of behavior therapy have shown some efficacy in the treatment of cocaine abusers. Relapse prevention skills training produced better outcomes than an intensity-matched comparison therapy, but these effects were only apparent during follow-up. This may be consistent with the intent of the treatment, if patients continued to utilize after treatment the skills they had been taught during treatment. In contrast, several controlled clinical trials support the efficacy of a community reinforcement approach and the voucher-incentive program for outpatient treatment of cocaine abuse. These therapies have produced impressive during-treatment results on measures of sustained cocaine abstinence. To date, evaluations of behavior therapy for cocaine abuse have, by and large, compared two or more treatments with equivalent intensity but different content. In the event that these treatments produce equivalent effects, it is not possible to know whether both are effective or neither is effective. One approach to improving behavior therapy methodology would be to include variations in the amount or intensity of a given therapy (including minimal contact delivery or wait-list comparisons). Intensity variation and/or a no-treatment control would allow firm conclusions to be drawn about the efficacy of the treatment of interest. It would also be beneficial to the treatment evaluation effort if all treatment studies in the future were to report a common set of outcome measures, including percent positive urine samples at regular in-treatment intervals, mean longest duration of continuous abstinence (urinalysis verified) during treatment, percentage of patients achieving a specified duration of abstinence (e.g., 8 weeks), self-reported days of drug use during and after treatment based on the Addiction Severity Index, and verified abstinence rates at 3- and 6-month follow-up.

Suggestions for Future Development and Evaluation Efforts

In this section, we speculate as to why medications that have shown promising results in controlled laboratory research have failed to show treatment efficacy when tested in outpatient clinical trials. Laboratory data suggest that the effects of cocaine may be altered by some medications; however, these medications have shown only partial efficacy, such that cocaine's effects may have been altered or attenuated but were not completely eliminated. An altered or weakened drug effect could result in reduced cocaine use, although it should be noted that an increase in use is an equally plausible outcome. In either event, there is a problem with detection of altered rates of cocaine use in clinical trials. Specifically, qualitative urine testing, the typical outcome measure used in clinical trials, is good at detecting the presence versus absence of a drug and verifying periods of drug abstinence but is notoriously insensitive to changes in drug use short of abstinence. Further, self-report data can be quite variable and unreliable. Therefore, it is possible that medications have actually produced benefits that simply went undetected in previous clinical trials. Improvements in the sensitivity of objective outcome measures need to be considered for future treatment evaluation work. Quantitative urine testing, for example (73), may be a more sensitive indicator of changes in rates and patterns of cocaine use.

The ability of clinical trials to detect beneficial medication effects may also interact with the type of concurrent behavior therapy employed. Cognitive behavior therapies such as relapse prevention may be helpful for maintaining long-term abstinence, but appear to lack robust procedures that can reliably produce periods of sustained short-term abstinence in most patients. Rather, motivation for abstinence is variable and dependent on the circumstances of the individual patient. These are the therapies that have been most often used in clinical trials for medication evaluations, including studies of smoking cessation treatment, where beneficial treatment interaction effects have been documented. However, in the case of cocaine treatment, it may also be useful to test medications in combination with more potent behavior therapies, such as community reinforcement, that provide uniform incentives to sustain drug abstinence. It is not likely that medications will instill motivation to stop drug use. However, it is possible that medications that weaken but do not eliminate the psychostimulant drug signal would promote even better outcomes under conditions where drug abstinence is motivated, in part, by uniform external incentive procedures.

Conclusions and Recommendations

Smoking cessation treatment provides a model by which treatment evaluation efforts for cocaine can proceed. In this model, the combination of two partially effective treatments—one behavioral and the other pharmacological substitution—has resulted in enhanced outcomes that are better than those produced by either treatment alone. If this model is valid for the treatment of other types of psychostimulant abuse and for other types of pharmacotherapies, we can expect that a combination treatment approach will ultimately be the most beneficial. At this juncture, it is not possible to recommend the particular pharmacological intervention that should be tested for efficacy with cocaine abuse. What can be recommended are strategies for evaluation that include randomized, double-blind testing of active versus placebo medications in combination with behavior therapies of varying type and intensity to establish separate and combined efficacy. In particular, it is recommended that medications, including those previously found ineffective when tested in combination with relapse prevention skills training therapies, be tested in combination with recently developed effective behavioral therapies that provide more potent and uniform external incentives for abstinence than has previously been the case. Finally, measurement issues need to be addressed, including reporting of a common set of outcome measures in clinical trials and consideration of qualitative (as opposed to quantitative) urine testing to provide a more sensitive assay that can detect reductions in drug use as well as complete drug abstinence.

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