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Integrating Behavioral Therapies With Medications in the Treatment of Drug Dependence

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Contents

Medications and Behavioral Therapies: The Whole May Be Greater Than the Sum of the Parts

Lisa Simon Onken, Jack D. Blaine, and John J. Boren

It is no revelation that drug dependence is a complex problem with behavioral, cognitive, psychosocial, and biological dimensions and may be treated with behavioral therapy (including behavior therapy, psychotherapy, and counseling), and, where available, pharmacotherapy. Drug use can be reduced behaviorally with appropriate manipulation of reinforcements within the environment (Higgins et al. 1993). Continued improvements over time in drug use can be initiated by cognitive-behavioral psychotherapies to modify cognitions that perpetuate drug use (Carroll et al., submitted for publication), and a reduced likelihood of relapse has been engendered by specialized training approaches (Rohsenow et al., in press). Methadone, of course, has long been recognized as an effective pharmacotherapy to reduce opiate use, and its biological mechanism of action is well understood.

Even though a complete understanding of drug dependence must address behavioral, psychosocial, cognitive, and biological issues, an effective treatment for an individual need not, in all cases, do so. Sometimes no treatment is necessary, as is evidenced by the veterans of Vietnam who tested positive for heroin while in Vietnam but showed no sign of addiction after returning home (Robins 1993). Many a baby boomer who experienced the drug culture of the late sixties and early seventies can attest to knowing more than a few seemingly addicted individuals who, without treatment, are now drug-free, upstanding members of the community.

Where treatment is required, integrated behavioral and pharmacological treatment is not always possible, practical, or necessary. For example, except for opiate, alcohol, and nicotine dependence, no medications exist. When behavioral treatments are the only treatments available, of course, there is no integration to be done. Even where medications exist, many individuals will not take them, and some individuals may be able to conquer their drug dependence with behavioral interventions alone. Finally, there may be compelling reasons to administer medication in the

absence of any behavioral or psychosocial services. Although controversial, some have argued that in this era of AIDS, methadone alone may be preferable to no treatment at all for a subgroup of opiate-addicted individuals awaiting more comprehensive treatment or as an initial step in a harm reduction approach.

So why a monograph on "Integrating Behavioral Therapies With Medications in the Treatment of Drug Dependence"? Two concepts drove this monograph and the technical review that led to this monograph. First, appropriate behavioral interventions can potentially interact effectively with medications, enhancing their effects. From the earliest days of methadone maintenance, Dole and Nyswander (1965) stressed the importance of combining psychosocial services with methadone, and there has been ample literature since then to support this point of view (Grabowski et al. 1993; McLellan et al. 1993; Stitzer et al. 1993). Similarly, behavioral interventions alone are sometimes insufficient to treat many drug abusers effectively, and it is believed that medications, whether for concomitant mental or physical disorders or for drug abuse per se, have a potential for improving the effect of behavioral treatments. One function of this monograph is to review the literature to date on combined behavioral and pharmacological treatments for drug dependence. The ultimate goal of this monograph is to shed light on the questions of when and how behavioral and pharmacological therapies for drug dependence can be integrated for optimal treatment outcome.

The participants in the technical review who spawned this monograph included the scientific editors of this monograph and Drs. Kathleen Carroll, John Docherty, Stephen Higgins, Kenneth Howard, John Hughes, Marsha Linehan, Charles P. O'Brien, Timothy O'Farrell, Stephanie O'Malley, Michael Otto, Bruce Rounsaville, and Roger Weiss. The technical review was held on June 10 and 11, 1993, preceding the annual College on Problems of Drug Dependence meeting in Toronto. The thoughts expressed at this meeting follow. It is hoped the contributions to this monograph will stimulate innovative research on the integration of pharmacological and behavioral therapies.

REFERENCES

Carroll, K.M.; Rounsaville, B.J.; and Nich, C. "One Year Follow-Up of Psychotherapy and Pharmacotherapy for Cocaine Abuse: Evidence for Continued Improvement After Psychotherapy." Manuscript submitted for publication.

Dole, V.P., and Nyswander, M.E. A medical treatment for diacetylmorphine (heroin) addiction. *JAMA* 193:646-650, 1965.

Grabowski, J.; Rhoades, H.; Elk, R.; Schmitz, J.; and Creson, D. Clinicwide and individualized behavioral interventions in drug dependence treatment. In: Onken, L.S.; Blaine, J.D.; and Boren, J.J., eds. *Behavioral Treatments for Drug Abuse and Dependence.* National Institute on Drug Abuse Research Monograph 137. DHHS Pub. No. (ADM)93-3684. Washington, DC: Supt. of Docs., U.S. Govt. Print. Off., 1993.

Higgins, S.T.; Budney, A.J.; Bickel, W.K.; Hughes, J.R.; Foerg, F.; and Badger, G. Achieving cocaine abstinence with a behavioral approach. *Am J Psychiatry* 150:5, 1993.

McLellan, A.T.; Amdt, I.O.; Metzger, D.S.; Woody, G.E.; and O'Brien, C.P. The effects of psychosocial services in substance abuse treatment. *JAMA* 269:1953-1959, 1993.

Robins, L. Vietnam veterans' rapid recovery from heroin addiction: A fluke or normal expectation. *Addiction* 88:1041-1054, 1993.

Rohsenow, D.J.; Monti, P.M.; and Abrams, D.B. Psychosocial assessment and coping skills treatment for cocaine abuse: Preliminary results, In: Tims, F.; Blaine, J.D.; Onken, L.S.; and Tai, B., eds. *Treatment of Cocaine Dependence: Outcome Research.* National Institute on Drug Abuse Research Monograph. Washington, DC: Supt. of Docs., U.S. Govt. Print. Off., in press.

Stitzer, M.L.; Iguchi, M.Y.; Kidorf, M.; and Bigelow, G.E. Contingency management in methadone treatment: The case for positive incentives. In: Onken, L.S.; Blaine, J.D.; and Boren, J.J., eds. *Behavioral Treatments for Drug Abuse and Dependence.* National Institute on Drug Abuse Research Monograph 137. NIH Pub. No. (ADM) 93-3684. Washington, DC: Supt. of Docs., U.S. Govt. Print. Off., 1993.

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Enhancing the Effectiveness of Methadone Using Psychotherapeutic Interventions

Charles P. O'Brien, George E. Woody, and A. Thomas McLellan

INTRODUCTION

The advent of maintenance treatment afforded the possibility that psychotherapeutic interventions could be applied to the problems of opiate addicts. Prior to methadone, heroin addicts showed little interest in psychotherapy. Attendance at drug-free outpatient programs was (and is) very irregular, and even the promise of free psychotherapy produced few takers and little evidence of efficacy (Nyswander et al. 1958). The availability of methadone in the early 1970s made heroin addicts available for psychotherapy, but there was controversy as to whether methadone, either for pharmacological or symbolic reasons, prevented engagement in psychotherapy (Boume 1975, pp. 1 l-l 2; Karkus 1973). There was also the perception that most heroin addicts had an antisocial personality and thus were not amenable to psychotherapy.

There has been great progress in this area over the past two decades. Much more is known about how to apply psychotherapy and who is likely to respond. This chapter is a selective summary of some of the significant studies that have led to this present state of knowledge in this area. Not all studies are included, but the representative examples illustrate the difficulties of studies in this population as well as what has been learned that can be applied by the clinician working in a methadone program.

CONTINUOUS MEASURES OF PRETREATMENT STATUS AND OUTCOME

It is obvious that patients are not likely to be "cured" by the addition of psychotherapy to methadone treatment. Thus, outcome by improvement must be measured relative to the patient's status at the beginning of treatment. To do this, measures of change must be used that are sensitive and that also take into account the many nondrug variables that impact on

the results of treatment. The Addiction Severity Index (ASI) was developed to assess a wide range of problem areas, and it is now in use around the world as both a clinical and research tool (McLellan et al. 1980). Using the ASI, differences can be documented among patients in such areas as medical, psychiatric, employment, family, and legal problems. These factors are important in themselves, and they significantly influence the response to any kind of treatment for drug dependence. Thus, while studies of methadone treatment have the advantage of urine tests as one objective measure of outcome, even this unbiased, objective measure of drug use will be affected by the status of the patient in several nondrug abusers. These nondrug factors are particularly important in comparing the results of studies involving different populations. Generally, better educated patients with more stable family, employment, and social situations have a better prognosis no matter what type of treatment is used.

Another variable that should be addressed in studies of psychotherapeutic interventions to enhance the effectiveness of methadone is the dose of methadone. Many programs use doses that are too low to stabilize the patient, to reduce drug craving, or to diminish the effects of injected heroin by cross-tolerance. The survey of 12 methadone programs by Ball and Ross (1991) showed a wide range across programs in average dose, and a strong negative correlation with the frequency of opiate-positive urines. For example, patients receiving less than 39 mg daily had a 3 1 percent probability of heroin use during the 30 days prior to evaluation; for those receiving 60 to 79 mg the probability was only 6 percent, and only 2 percent of those receiving 80 to 100 mg used heroin during the prior 30 days. While it is generally accepted that dose requirements may vary among patients, some treatment programs have adopted the philosophy that lower doses are preferable. The Ball and Ross data as well as more than 10 studies in the United States and the world indicate that this philosophy is associated with higher rates of supplementation by street heroin. Thus, in order to study the effects of a psychotherapeutic intervention such as psychotherapy or contingency contracting among methadone patients, it is first necessary to be certain that all patients in the study are receiving an adequate dose of methadone.

FAMILY THERAPY

One of the earliest controlled studies of psychotherapy in methadone patients was conducted at the University of Pennsylvania/Veterans

Administration (VA) program in Philadelphia, involving structural family therapy (Stanton et al. 1982). Structural family therapy was reasonably well defined, and the therapists were all experienced and supervised by leaders in the family therapy field. The subjects were heroin addicts in methadone treatment who were regularly involved with their families of origin. The patients were randomly assigned to one of four treatment/ control conditions: family therapy with monetary reward to all family members for clean urines from the index patient; family therapy with no rewards for clean urine; family meetings to watch a control video (travel to other cultures) with the same monetary reward for clean urines; and methadone with individual counseling (standard treatment). The monetary reward was $5 per clean urine in the mid 1970s which was the equivalent of about $15 in current dollars. This may have been the earliest report of a study using monetary rewards for clean urines. The results indicated a significant effect for the groups randomly assigned to family therapy whether or not they received monetary rewards. The order of success at l-year followup was family therapy with reward, family therapy without reward, family movie with reward, and standard treatment. The results were evident on measures of use of opiate and nonopiate drugs, but not on work-school performance or alcohol use.

Although the controlled study of family therapy produced positive results, the technique lacked practical appeal to the experienced busy therapists in the program. It was extremely difficult to engage these families in therapy. It took many personal appeals on the part of the therapists to get the therapy started. Thus, in practice, family therapy has been reserved for those patients who have significant family problems and whose families are willing to enter therapy. Despite this caveat, family therapy remains a useful option, and it is helpful to have at least one therapist on the staff who has special training in this area.

INDIVIDUAL PSYCHOTHERAPY

Individual psychotherapy is of interest because of clinical observations that some drug users begin the use of heroin and other drugs in an effort to decrease symptoms of a psychiatric disorder. While many studies have shown that more than 60 percent of patients in methadone treatment have psychiatric diagnoses in addition to opiate dependence, it is not clear whether these disorders began before or after the initiation of drug abuse. These “dual diagnosis” patients could be appropriate candidates for psychotherapy if it were available. At issue is the funding of methadone

programs at a level sufficient to provide for professionally trained psychotherapists. The largest study that addressed the efficacy of psychotherapy as compared to counseling by nonprofessional therapists involved two different kinds of psychotherapy (Woody et al. 1983). The first type of therapy, cognitive behavioral (CB) therapy, is an active, directive, time-limited system of psychotherapy that focuses on uncovering automatic thoughts and assumptions underlying problematic behavior. Techniques include making lists, homework, role playing, and other cognitive and behavioral methods. A CB treatment manual for opiate addiction was developed for the study and eventually was published as a book (Beck et al. 1993).

The other type of therapy used in the study was supportive-expressive (SE) therapy. It is analytically oriented and nondirective, and its goals are to help the patient identify and work through problematic relationship themes. A manual for this type of therapy also was developed and published as a book (Luborsky 1984). Drug counseling (DC) also was operationalized, and a manual was written. The major focus of DC is on identifying specific practical problems, encouraging cessation of drug use, and providing external services rather than dealing with intrapsychic processes. All three types of treatment were administered according to their respective manuals, and therapists met weekly with a supervisor to monitor adherence to the specific techniques. Sessions were taped and rated by independent judges for compliance with the characteristics of each treatment.

The subjects were 110 methadone patients beginning a new course of treatment. They were randomly assigned to DC alone or DC plus either SE or CB. Thus, all patients received DC, but two-thirds received professional psychotherapy in addition to counseling. The results showed that patients in all three groups showed improvement across most outcome measures, but those randomly assigned to psychotherapy showed more and larger gains than those receiving DC alone (Woody et al. 1983). The most significant psychotherapy effects were demonstrated in the patients with significant psychiatric problems in addition to opiate dependence. Patients with severe psychiatric problems receiving DC alone showed little or no improvement. In contrast, patients in this category assigned to either SE or CB showed significant gains in many areas in addition to less use of heroin and other illegal drugs (Woody et al. 1984). The dose of methadone functioned as a dependent variable because patients and their counselors could ask for a raise if the patients were not doing well. This process resulted in the DC patients getting

more dose increases and thus a higher methadone dose than the professional therapy groups. Ancillary medications such as anti-depressants could be prescribed when necessary by psychiatrists not involved in the psychotherapy. Such prescriptions were needed significantly less often by patients in the two psychotherapy groups. There were few significant outcome differences between SE and CB therapy groups. SE patients showed more improvement in psychological functioning and employment, while CB patients showed more improvement with legal problems.

While the above study showed clear benefits for the addition of psychotherapy to methadone treatment, another large study (n = 72) failed to show an effect using short-term interpersonal psychotherapy (IPT) (Rounsaville et al. 1983). There were, however, major differences in the organization of the two studies. While Woody and colleagues used psychotherapists as members of the staff who were readily available at the methadone site, Rounsaville used therapists who were compensated by the hour as methadone patients kept appointments at their private offices. Only 5 percent of their eligible patients agreed to participate, and 50 percent of these completed treatment. Woody and colleagues found that 60 percent of their patients were interested in the study and 60 percent of these became engaged in treatment. It appeared that having the psychotherapy study central to the clinic was an important factor in patient engagement and retention.

Subsequently, the authors' group has completed two additional studies of psychotherapy in methadone patients. One utilized SE therapy as a comparison with cue extinction for methadone patients. The rationale for the extinction procedure is contained in the rich literature demonstrating both in animals and in humans that opiates and several other drugs of abuse are capable of producing conditioned reflexes that persist after cessation of drug taking (O'Brien 1975; O'Brien et al. 1977; Wikler 1973). It was found that conditioned responses can be elicited in opiate addicts even when they are maintained on methadone (McLellan et al. 1986). When presented with stimuli previously associated with the use of heroin, many methadone-treated patients report craving for opiates and exhibit physiological arousal consistent with opiate withdrawal signs. It is difficult to demonstrate experimentally that this phenomenon actually provokes drug taking, but based on the strength and prevalence of their responses, and the clinical reports of patients, it was postulated that extinguishing or reducing these responses might improve the clinical outcome of patients in methadone treatment (Childress et al. 1986a,

1986b). Stabilized methadone patients were randomly assigned to SE alone, extinction plus SE, counseling alone, or counseling plus extinction. As in the original psychotherapy study (Woody et al. 1983), the patients receiving professional psychotherapy with or without extinction showed significantly more improvement on the ASI than the group receiving only extra drug counseling.

A third study of psychotherapy in methadone patients has recently been completed in two methadone programs in the Philadelphia community (Woody et al. 1994). An objective of this study was to determine whether the effectiveness of psychotherapy with patients showing psychiatric symptoms could be demonstrated in community methadone programs not as richly staffed as the University of Pennsylvania/VA program. The design of this study also was more balanced than in the original study. Newly admitted methadone maintenance patients were randomly assigned to standard drug counseling plus either SE or an additional counselor so that all patients received equivalent attention from a helping person. The findings are in the process of being published elsewhere, so details will not be included. It can be reported, however, that the setting was less organized than in the University of Pennsylvania/VA setting and less conducive to a study of psychotherapy. About 40 percent of urine tests were positive for opiates, but there was inconsistent feedback about positive urines to patients since the basic treatment required only one urine test per month. Study patients had' weekly urine tests, but the results were not available to clinic staff. In this setting, the patients randomly assigned to SE treatment still showed significantly greater improvement than those assigned to the counseling control group in the areas of drug use, employment, and psychiatric symptoms. There was a trend toward lower methadone doses in the psychotherapy group. The magnitude of the positive changes was approximately as great as those seen in studies conducted in the authors' clinic; however, the major advantages for the psychotherapy group were not achieved until the 12-month followup point (6 months after the end of the therapy). These findings are interpreted as showing a positive though transient effect of adding the second counselor to the control group. The improvements produced by the professional psychotherapy were more lasting, and thus there were greater differences between psychotherapy and control groups at 12 months than at 6 months.

CONTINGENCY CONTRACTING

The treatment of drug dependence has a distinct advantage over treatment in most other areas because an objective measure of progress is available-the urine test. While there are limits to the information gained from urine testing by itself, it does provide accurate evidence of recent drug use. Urine testing is quite practical in methadone programs because patients come to the clinic regularly and urines, monitored by direct observation or by temperature checks, can be collected. Most methadone programs have had rules requiring negative urine tests for abused drugs as a contingency for receiving take-home doses of methadone since the programs began in the late 1960s and early 1970s. Unfortunately, the consequences of the positive urine tests are generally distant in time from the behavior and often not consistently applied. In order to save money, methadone programs are obtaining fewer urine tests (eight per year required) and not incorporating the results into the counseling sessions.

A number of studies have experimentally examined the effects of contingent reinforcement of clean urines. Rapid monetary reinforcement of clean urines was applied in the mid 1970s for the family therapy study discussed above (Stanton et al. 1982), but no significant effects of the payments to family members and to index patients were observed. More recently there have been a series of controlled studies using contingency contracting based on urine test results that have resulted in at least temporary behavior change. Stitzer and colleagues (1992) used take-home privileges for methadone patients as the reinforcement for 2 consecutive weeks of drug-free urines. The contingent procedure produced more individuals with at least 4 consecutive weeks of abstinence (32 percent versus 8 percent) than the control group that received take-home doses independent of urine tests. When nonresponders in the noncontingent group were switched to the contingency, 28 percent achieved abstinence. The best predictor of success in this procedure was low baseline levels of drug use. Other researchers have reported similar results using take-home doses of reinforcers for abstinence (Milby et al. 1978). These studies strongly support the clinical practice of rewarding patients with take-home doses when they produce clean urines. The 2-week period used in the study allows more flexibility and is likely to be more effective than the 3-month waiting period for take-home doses required by most programs.

Supplementation of methadone dose by nonopiate drugs such as cocaine and benzodiazepines also has been addressed by contingency contracting.

Contingent take-home doses of methadone have been used successfully to reduce benzodiazepine supplementation (Iguchi et al. 1988; Stitzer et al. 1982). Temporary abstinence from benzodiazepines was observed in about 50 percent of the patients during the 12- to 20-week contingent take-home period. In the recent study by Stitzer and colleagues (1992) noted above, unprescribed use of benzodiazepines and cocaine responded equally to the contingency condition. Magura and colleagues (1988), using take-home doses as the reinforcer, found no overall differences between the percentage of positive urines between the contingency and precontingency periods and between the contingency and postcontingency periods. This group concluded that contracting had a favorable, though transient effect, only on noncocaine-abusing methadone patients.

The problem of cocaine abuse among methadone patients was the focus of a recent study by Silverman and colleagues (1994) using vouchers exchangeable for retail items as a reinforcer. This is the contracting system developed by Higgins and colleagues (1991) to achieve abstinence in primary cocaine addicts. Silverman provided vouchers to 19 methadone patients contingent on cocaine-negative tests. A matched control group was yoked to the contingent group and thus received the same number of vouchers, but not contingent on their behavior. Cocaine use was substantially reduced in the contingent group, but not in the control group over an 8-week period. Although the reinforcement of using vouchers for clean urines is more appealing than reinforcement with cash, there remain substantial practical obstacles to the general employment of this technique for publicly funded methadone programs.

Dose of methadone also has been used as a reinforcer. For example, Stitzer and colleagues (1986) reported that polydrug supplementation could be reduced when methadone dose was increased as a reward for drug-free urines and when methadone dose was decreased as a consequence of drug-positive urines. During a study of ambulatory methadone detoxification, Higgins and colleagues (1986) gave patients the option to increase their methadone dose by up to 20 mg contingent upon opiate-free urines. Another group had the option to similarly increase their dose on a noncontingent basis. Only the contingent group showed suppression of opiate use outside of the methadone program.

There are practical problems in using methadone dose increases as a reward and decreases as a form of punishment. First, it seems at odds with the concept that patients on methadone should receive an adequate

dose to produce physiological stability, to reduce or eliminate craving for opiates, and to produce cross-tolerance to street opiates such that their effects are drastically diminished. This concept is supported by the Ball and Ross (1991) data showing the inverse relationship between dose and frequency of urines positive for opiates. According to these data, patients with positive urines whose doses are in the lower range should be increased to the 60 to 100 mg range to see if the higher dose eliminates the problem. Using extra methadone as a reward for clean urines would seem to reinforce the use of methadone as a euphorigenic substance and thus highlight its potential for abuse. Punishing dirty urines by dose reductions might make the problem worse if the patient actually "needed" a higher dose.

There also are ethical issues involved, as discussed by Nolimal and Crowley (1990). While these investigators noticed improvement during the first month of a contract involving dose reductions for positive urines, the effect faded in the second and third months. Of their 14 patients, 5 continued abuse and were terminated from methadone treatment. Termination from treatment also was a consequence of other studies using dose reduction as a contingency (Dolan et al. 1985; Saxon et al. 1993). This outcome is especially problematic in view of the accumulating evidence that even suboptimal methadone treatment is associated with protection from HIV infection (Metzger et al. 1993) and probably from other infections. Thus, forced termination from methadone for patients who are not disruptive to the program, but whose only infraction is some degree of continued opiate use, is ethically debatable.

Contingency contracting also has been used to address another common problem among patients in methadone treatment, that of alcohol abuse and alcoholism. Liebson and colleagues (1978) used methadone as a reinforcer to obtain disulfiram ingestion by severely alcoholic methadone patients. Of course, disulfiram blocks the metabolism of alcohol resulting in acetaldehyde production and a very unpleasant reaction when any alcohol is ingested. The protocol worked so well for Liebson and colleagues that it was used as the prototype for a large multiclinic trial of the treatment of alcoholic methadone patients (Ling et al. 1983). In the large sample, there were no differences between those randomly assigned to disulfiram or placebo. It appeared that focusing on the drinking behavior with breathalyzer tests and a contingency contract was enough to suppress drinking behavior in most of the methadone patients whether or not they actually received active disulfiram. Of course, use of the

breathalyzer alone has the advantage of not exposing the patient to the potential side effects of disulfiram ingestion.

DO COUNSELING AND PSYCHOTHERAPY ADD ANYTHING TO METHADONE?

The funding of public methadone programs naturally is limited, and there is always pressure to treat more patients for less money. Counseling and psychotherapy are relatively expensive components of methadone programs; thus it is reasonable to ask whether they are necessary. A study that directly addresses these questions was conducted in Philadelphia (McLellan et al. 1993), where patients in methadone treatment on a minimum of 60 mg were randomly assigned to one of three treatment conditions. The minimal contact group received methadone alone with no required counseling. Specific requests for information, referral, or dose change were dealt with as needed. The group randomized to standard treatment met weekly with their counselors and more often as needed. The group assigned to enhanced treatment had, in addition to sessions with their counselors, access to psychiatric treatment, as well as employment and family therapy sessions. In reality, few of the minimal contact patients could be given as little treatment as the protocol proposed. Sixty-nine percent of the minimal contact patients had to be "rescued" from the study because of eight consecutive positive urines. This "safety net" was included in the protocol for ethical reasons since the patients randomized to minimal contact were receiving less than standard care. On virtually all outcome measures including drug use, psychological status, family problems, and other factors on the ASI, there was a dose-response relationship between amount of psychosocial and ancillary services and improvement. Since there was no nontreatment, the study could not address how much benefit there was in methadone alone as compared to the use of heroin on the street. It did demonstrate clearly, however, that the benefits of methadone were much greater for the patients receiving standard weekly counseling sessions and significantly greater still for patients randomized to the enhanced therapy condition.

SUMMARY

There is consistent evidence that the efficacy of methadone can be enhanced by psychotherapeutic interventions. For individual

psychotherapy, the increased efficacy is most demonstrable among methadone patients also suffering from psychiatric disorders. Patients with severe psychiatric problems generally show little response to drug counseling alone. There is no evidence of a consistent advantage of one type of psychotherapy over another. Contingency contracting using take-home doses of methadone to reinforce drug-free urines has been shown to be effective, at least over the short term. Rewarding clean urines by vouchers exchangeable for retail items is supported by a growing experimental database, although practical issues remain for publicly funded methadone programs. The use of methadone dose as a reinforcer has shown some efficacy, but there are both ethical and conceptual problems. Finally, while there are likely to be some benefits from simply administering methadone alone in the most economical way, the available evidence clearly shows that a relatively minor investment in counseling, individual psychotherapy, or contingency contracting can result in major improvements in the results of this medication.

REFERENCES

Ball, J.C., and Ross, A. *The Effectiveness of Methadone Maintenance Treatment.* New York: Springer-Verlag, 1991.

Beck, A.T.; Wright, F.D.; Newman, C.F.; and Liese, B.S. *Cognitive Therapy of Substance Abuse.* New York: Guilford Press, 1993.

Boume, P.G. *Methadone: Benefits and Shortcomings.* Washington, DC: Drug Abuse Council, Inc., 1975.

Childress, A.R.; McLellan, A.T.; and O'Brien, C.P. Abstinent opiate abusers exhibit conditioned craving, conditioned withdrawal and reductions in both through extinction. *Brit J Addict* 81:655-660, 1986b.

Childress, A.R.; McLellan, A.T.; and O'Brien, C.P. Conditioned responses in a methadone population: A comparison of laboratory, clinic and natural setting. *J Subst Abuse Treat* 3:173-179, 1986a.

Dolan, M.P.; Black, J.L.; Penk, W.E.; Robinowitz, R.; and DeFord, H.A. Contracting for treatment termination to reduce illicit drug use among methadone maintenance treatment failures. *J Consult Clin Psychol* 53(4):549-551, 1985.

Higgins, S.T.; Delaney, D.D.; Budney, A.J.; Bickel, W.K.; Hughes, J.R.; Foerg, F.; and Fenwick, J.W. A behavioral approach to achieving initial cocaine abstinence. *Am J Psychiatry* 148(9):1218-1224, 1991.

Higgins, S.T.; Stitzer, M.L.; Bigelow, G.E.; and Liebson, I.A. Contingent methadone delivery: Effects on illicit opiate use. *Drug Alcohol Depend* 17(4):311-322, 1986.

Iguchi, M.Y.; Stitzer, M.L.; Bigelow, G.E.; and Liebson, I.A. Contingency management in methadone maintenance: Effects of reinforcing and aversive consequences on illicit polydrug use. *Drug Alcohol Depend* 22:1-7, 1988.

Karkus, H.D. Methadone vs. psychotherapy in the treatment of addiction. *Int J Addict* 8:427-434, 1973.

Liebson, I.A.; Tommasello, A.; and Bigelow, G.E. A behavioral treatment of alcoholic methadone patients. *Ann Intern Med* 89(3):342-344, 1978.

Ling, E.; Weiss, D.G.; Charuvastra, C.V.; and O'Brien, C.P. The use of disultiram for alcoholics on methadone maintenance. *Arch Gen Psychiatry* 40:851-854, 1983.

Luborsky, L. *Principles of Psychoanalytic Psychotherapy: A Manual for Supportive-Expressive (SE) Treatment.* New York: Basic Books, 1984.

Magura, S.; Casriel, C.; Goldsmith, D.S.; Strug, D.L.; and Lipton, D.S. Contingency contracting with polydrug-abusing methadone patients. *Addict Behav* 13(1):113-118, 1988.

McLellan, A.T.; Amdt, 1.0.; Metzger, D.S.; Woody, G.E.; and O'Brien, C.P. The effects of psychosocial services in substance abuse treatment. *JAMA* 269(15):1953-1959, 1993.

McLellan, A.T.; Childress, A.R.; Ehrman, R.; and O'Brien, C.P. Extinguishing conditioned responses during opiate dependence treatment turning laboratory findings into clinical procedures. *J Subst Abuse Treat* 3:33-40, 1986.

McLellan, A.T.; Luborsky, L.; O'Brien, C.P.; and Woody, G.E. Improved diagnostic instrument for substance abuse patients: The Addiction Severity Index. *J Nerv Ment Dis* 168:26-33, 1980.

Metzger, D.S.; Woody, G.E.; McLellan, A.T.; O'Brien, C.P.; Druley, P.; Navaline, H.; DePhilippis, D.; Stolley, P.; and Abrutyun: E. Human immunodeficiency virus seroconversion among intravenous drug users in and out of treatment: an 18 month prospective follow-up. *J Acquir Immune Defic Syndr* 6:1049-1056, 1993.

Milby, J.B.; Garrett, C.; English, C.; Fritschi, 0.; and Clarke, C. Take-home methadone: Contingency effects on drug-seeking and productivity of narcotic addicts. *Addict Behav* 3(3-4):215-220, 1978.

Nolimal, D., and Crowley, T.J. Difficulties in a clinical application of methadone-dose contingency contracting. *J Subst Abuse Treat* 7(4):219-224, 1990.

Nyswander, M.; Winick, C.; Bernstein, A.; Brill, L.; and Kaufer, G. The treatment of drug addicts as voluntary outpatients: A progress report. *Am J Orthopsychiatry* 28:714-729, 1958.

O'Brien, C.P. Experimental analysis of conditioning factors in human narcotic addition. *Pharmacol Rev* 27:535-543, 1975.

O'Brien, C.P.; Testa, T.; O'Brien, T.J.; Brady, J.P.; and Wells, B. Conditioned narcotic withdrawal in humans. *Science* 195:1000-1002, 1977.

Rounsaville, B.J.; Glazer, W.; Silber, C.H.; Weissman, M.M.; and Kleber, H.D. Short-term interpersonal psychotherapy in methadone-maintained opiate addicts. *Arch Gen Psychiatry* 40:629-636, 1983.

Saxon, A.J.; Calsyn, D.A.; Kivlahan, D.R.; and Roszell, D.K. Outcome of contingency contracting for illicit drug use in a methadone maintenance program. *Alcohol Drug Depend* 31(3):205-214, 1993.

Silverman, K.; Schuster, C.R.; Brooner, R.K.; Montoya, I.D.; and Preston, K.L. 'Contingency Management of Cocaine Use in a Methadone Maintenance Program." Paper presented at the annual meeting of the College on Problems of Drug Dependence, Palm Beach, June 21, 1994.

Stanton, M.D.; Todd, T.C.; Steier, F.; Van Dusen, J.M.; and Cook, L. *The Family Therapy of Drug Abuse and Addiction.* New York: Guilford Press, 1982.

Stitzer, M.L.; Bickel, W.K.; Bigelow, G.E.; and Liebson, I.A. Effect of methadone dose contingencies on urinalysis test results of polydrug-abusing methadone-maintenance patients. *Alcohol Drug Depend* 18(4):341-348, 1986.

Stitzer, M.L.; Bigelow, G.E.; Liebson, I.A.; and Hawthorne, J.W. Contingent reinforcement for benzodiazepine-free urines: Evaluation of a drug abuse treatment intervention. *J App Behav Anal* 15(4):494-503, 1982.

Stitzer, M.L.; Iguchi, M.Y.; and Felch, L.J. Contingent take-home incentive: Effects on drug use of methadone maintenance patients. *J Consult Clin Psychol* 60(6):927-934, 1992.

Wikler, A. Dynamics of drug dependence: Implications of a conditioning theory for research and treatment. *Arch Gen Psychiatry* 28:611-616, 1973.

Woody, G.E.; Luborsky, L.; McLellan, A.T.; O'Brien, C.P.; Beck, A.T.; Blaine, J.; Herman, I.; and Hole, A. Psychotherapy for opiate addicts: Does it help? *Arch Gen Psychiatry* 40:639-645, 1983.

Woody, G.E.; McLellan, A.T.; Luborsky, L.; and O'Brien, C.P. "Psychotherapy in Community-Based Methadone Programs: A Follow-Up Study." Paper presented at annual meeting of North American Society for Psychotherapy Research, Santa Fe, NM, February 6, 1994.

Woody, G.E.; McLellan, A.T.; Luborsky, L.; O'Brien, C.P.; Blaine, J.; Fox, S.; Herman, I.; and Beck, A.T. Severity of psychiatric symptoms as a predictor of benefits from psychotherapy: The Veterans Administration-Penn study. *Am J Psychiatry* 141(10):1172-1177, 1984.

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Integrating Psychotherapy and Pharmacotherapy for Cocaine Dependence: Results From a Randomized Clinical Trial

Kathleen M. Carroll, Bruce J. Rounsaville, Charla Nich, Lynn Gordon, and Frank Gawin

To date, research on treatment for cocaine dependence has focused on either psychosocial or pharmacotherapeutic approaches, and neither the relative effectiveness of both forms of treatment nor the potential benefits of combined treatments have been the focus of a single trial. For example, pharmacological trials have tended to evaluate the efficacy of medications against a background of psychosocial treatments that are intended to enhance treatment retention and medication compliance. However, because the effectiveness of nonpharmacologic aspects of treatments is not of primary interest in such studies, psychosocial components of treatment are rarely specified or implemented according to current standards of psychotherapy research. That is, little attention usually is given to treatment manuals, training and selection of appropriate therapists, monitoring therapists' delivery of treatment, or patient compliance with psychosocial aspects of treatment.

Lack of specification of nonpharmacologic aspects of treatment in pharmacotherapy trials with cocaine abusers has several implications. First, the role or effectiveness of psychosocial treatments in enhancing treatment retention, medication compliance, or reduction of drug use cannot be examined in such studies. Second, because variations in the "psychosocial ground" against which pharmacologic agents are evaluated may result in variations in their effectiveness (Klerman 1975, pp. 67-81) across different studies, lack of specification of psychosocial treatments in pharmacologic trials for cocaine dependence may impede meaningful comparison of medication effects across studies (Carroll 1993). Variations in level and type of psychosocial treatments, as well as sample characteristics, may underlie much of the variation seen in drug effects across studies (Levin and Lehman 1991). Third, the specification of psychosocial treatments, which requires training of appropriate therapists and monitoring their delivery of treatment, may enhance their effectiveness (Rounsaville et al. 1988). Thus, studies that have not done

so may underestimate the potential effectiveness of psychosocial treatments for cocaine dependence.

Similarly, studies of psychotherapeutic treatments for cocaine abusers that have not utilized standard methods of psychotherapy research have both failed to show psychotherapy effects and have produced findings that are difficult to interpret (e.g., Kang et al. 1991). On the other hand, studies that have used these features have suggested the efficacy of behavioral over standard treatment (Higgins et al. 1993) and the specific efficacy of cognitive behavioral treatment for high-severity cocaine users (Carroll et al. 1991 a). Furthermore, no studies have evaluated how psychotherapy outcomes might be enhanced by effects of specific pharmacologic agents or even by placebo effects. For example, cocaine abusers' expectations for pharmacologic effects may enhance retention in the early stages of psychotherapy, where attrition may be high or the therapeutic relationship is still fragile.

STATE-TRAIT DISTINCTIONS

The variations in severity of cocaine abusers who present for treatment, the multidimensionality of cocaine abusers' problems, and the heterogeneity of cocaine abusers presenting for treatment suggest the potential value of evaluating and combining psychotherapy and pharmacotherapy. For example, Extein and Bowers (1979) differentiate between state disorders, described as time-limited, autonomous, and unresponsive to psychotherapeutic intervention (such as acute psychosis or delirium), and trait disorders, defined as "dysfunctional qualities which individuals tend to develop and carry throughout life and which become manifest as predictable patterns for interaction and response to stress" (Extein and Bowers 1979, pp. 690-691), such as personality disorders.

Cocaine dependence (and other forms of substance dependence) can be conceived as having attributes of both state and trait disorders, in varying degrees among different abusers. Pharmacotherapy or other forms of medical intervention are generally essential when "state" aspects are present (such as withdrawal symptoms associated with physical dependence, co-morbid Axis I disorders, or cocaine-induced organic mental disorders), as these would not be expected to respond to psychotherapy. Similarly, psychotherapy may be indicated for "trait" aspects of cocaine dependence upon which pharmacotherapy would be expected to have little impact (e.g., fostering motivation to reduce

substance use, restricting availability of cocaine, avoidance of situations associated with use, development of noncocaine-using social supports).

With a state/trait model of substance use disorders, the unique action of each particular approach can be investigated toward developing a more comprehensive model of treatment that recognizes the importance of heterogeneity among cocaine abusers. At lower severity levels and in the absence of state disorders, psychotherapy alone may be adequate. At higher levels of severity, the presence of state disorders may indicate the need for a combination of psychotherapy and pharmacotherapy, although in some cases the state disorder may be so dominant that it may be futile to initiate psychotherapy until the patient is stabilized and becomes available for psychotherapy (Carroll 1993).

ADVANTAGES OF COMBINING PSYCHOTHERAPY AND PHARMACOTHERAPY

There are several potential advantages of combining psychotherapy and pharmacotherapy for cocaine dependence. First, if psychotherapy is conceived and implemented in an active rather than a supportive role (that is, administered at full strength), it is more likely that maximal effects of psychotherapy will emerge and be detected. Psychotherapy and pharmacotherapy are assumed to work through different mechanisms (e.g., desipramine to reverse cocaine-induced neuroadaptation and psychotherapies such as relapse prevention skills training to improve an abuser's ability to cope with or avoid high-risk situations and relapse) and to affect different symptom areas. Thus, a major potential advantage of psychotherapy-pharmacotherapy combinations in which the integrity of each treatment is protected is that integrative treatments may improve outcome for more symptom areas than either treatment alone. Assuming psychotherapy and pharmacotherapy affect different symptom areas, by increasing the number of symptom areas potentially improved through combination treatments, one may dramatically improve the "hit rate" among cocaine abusers, who typically present with heterogeneity of symptoms and problems. Such a model also allows for detection of treatment specificity and so would guide future efforts toward patient-treatment matching.

Another advantage of evaluating combination treatments is that potential drawbacks associated with either treatment may be offset by the other. For example, the provision of support through psychotherapy may reduce

the potential negative impact of side effects arising from most pharmacotherapies. Similarly, instillation of hope through administration of a drug may support continuing participation in treatment during the early stages of treatment where a developing therapeutic alliance may be fragile or until coping skills are mastered and integrated (Carroll 1993).

In this chapter, data will be presented from a recently completed clinical trial that evaluated psychotherapy and pharmacotherapy, alone and in combination, as treatment for ambulatory cocaine abusers (Carroll et al. 1994a). In contrast to previous treatment efficacy studies with ambulatory cocaine abusers, the authors sought to give both psychotherapy and pharmacotherapy a "fair trial," that is, to: (1) protect the integrity of both forms of treatment through specification of delivery of psychotherapy and pharmacotherapy in manuals, (2) recruit and train therapists who were experienced in and committed to the type of treatment they performed in the trial, (3) closely monitor delivery of both forms of treatment throughout the trial (e.g., through plasma levels for medication and process assessment of session videotapes for psychotherapy), (4) allow adequate duration of treatment for emergence of effects of both psychotherapy and pharmacotherapy, (5) include assessments intended to tap specific effects of both forms of treatment, (6) select appropriate control conditions for both forms of treatment, and (7) use independent clinical evaluators who were blind to both forms of treatment to make ratings of primary outcomes.

METHODS

Subjects

Subjects were recruited from individuals seeking treatment at the Substance Abuse Treatment Unit of the Connecticut Mental Health Center in New Haven, CT, and from respondents to newspaper advertisements or public service announcements. Subjects were included who met current Diagnostic and Statistical Manual-III-R (DSM-III-R) criteria for cocaine dependence and who had used at least 12 g of cocaine during the past 3 months. Individuals were excluded who (1) were currently physically dependent on opiates, barbiturates, or alcohol, or whose principal drug of dependence was not cocaine; (2) met current DSM-III-R criteria for an Axis I disorder other than depressive or anxiety disorders, met lifetime criteria for schizophrenia or mania, or expressed significant current suicidal or homicidal ideation; (3) had a current

medical condition that would contraindicate ambulatory tricyclic antidepressant therapy; (4) had been treated for substance use during the previous 2 months or who were currently involved in psychotherapy or pharmacotherapy for any other psychiatric disorder; or (5) had conditions of probation or parole requiring reports of drug use to officers of the court.

Therapists

Therapists were 11 doctoral-level therapists (7 psychiatrists and 4 psychologists) who saw an average of 11 patients (range 1 to 23). Therapists selected were experienced in and committed to the type of treatment they conducted in the trial. All therapists received extensive training, which included successful completion of at least one closely supervised training case. To assure adherence to manual guidelines and to prevent drift through the main phase of the study, therapists in each condition met weekly with study investigators to discuss case material and review session videotapes.

Treatments

Each of the study treatments was manual-guided and delivered to patients in weekly individual sessions offered over 12 weeks. All training and main phase sessions were videotaped for supervision and process assessment. Evaluation of session videotapes by raters blind to treatment condition using an adaptation of the Collaborative Study Psychotherapy Rating Scale (Hill et al. 1992) showed the treatments were discriminable (Carroll et al. 1994b).

Desipramine. Subjects received an average of 200 mg/day of desipramine (or four placebo pills) to a maximum dose of 300 mg/day. Initial target plasma level ranges were 140 to 200 ng/mL. Dosage adjustments were made by nonblind study psychiatrists in response to serum blood levels and reported side effects, and these were yoked to dose changes for subjects receiving placebo to maintain a medication double blind.

Cognitive Behavioral Coping Skills Training. The cognitive behavioral treatment was based on Marlatt's Relapse Prevention (Marlatt and Gordon 1985) and adapted for use with cocaine users (Carroll et al. 1991 b). The goal of this treatment was abstinence from cocaine and other substances though identification of high-risk situations for relapse

and the implementation of effective coping strategies, which included fostering resolution to stop cocaine use through exploring positive and negative consequences of continued use, self-monitoring to identify high-risk situations for relapse, and the development of strategies for coping with and avoiding cocaine craving and high-risk situations.

Clinical Management. Clinical management was adapted from the guidelines developed for the National Institute of Mental Health (NIMH) Collaborative Study on the Treatment of Depression by Fawcett and colleagues (1987). The provision of clinical management was intended to provide (1) nonspecific elements of a psychotherapeutic relationship, including a supportive doctor-patient relationship, education, empathy, and the instillation of hope, without providing active ingredients specific to relapse prevention treatment, (2) medication management and opportunity to monitor patients' clinical status, and (3) a convincing therapeutic rationale, greater retention in the protocol, and compliance with medication.

Outcome Assessment

Patients were assessed before treatment, weekly during treatment, at posttreatment, and at followup interviews conducted 1, 3, 6, and 12 months after termination by an independent clinical evaluator who was blind to both the psychotherapy and pharmacotherapy condition. From the perspective of the blind clinical evaluators, procedures intended to protect the psychotherapy blind were only modestly effective but comparable to standard procedures used to maintain pharmacotherapy blinds (Carroll et al. 1994b).

Primary outcome measures were reduction in frequency of cocaine use (percentage of days the subject reported using cocaine while in treatment) and duration of longest period of consecutive abstinence. Patient self-reports were verified through urine toxicology screens, which were obtained at every visit. Of 622 urinalyses conducted, 7 1 percent were consistent with patient self-report, 15 percent were negative for cocaine although the patient reported recent cocaine use, and 14 percent were positive for cocaine in cases where the patient had denied use. In cases of discrepancy between self-report and toxicology reports, the source of data that indicated cocaine use was used in outcome analyses.

Secondary Outcomes. The Addiction Severity Index (ASI) (McLellan et al. 1980) was administered monthly during treatment to assess

multidimensional aspects of outcome and general functioning. The drug abuse section of the ASI was supplemented in order to calculate separate composite scores for cocaine versus other drugs, resulting in eight, rather than seven, outcome domains.

RESULTS

Sample Description

There were 139 patients determined to be eligible and randomized to treatment; of these, 121 (87 percent) began treatment and 110 (80 percent) completed two sessions or more. Of the 110 who were exposed to two or more sessions and took medication at least one week, 30 (27 percent) were women, 59 (54 percent) were minority, 78 (7 1 percent) were single or divorced, and 58 (52 percent) were working full- or part-time. Thirty-eight (34 percent) had some college education, 46 (42 percent) were high-school graduates, and 26 (24 percent) did not complete high school. The mean age of the sample was 28.8 years (SD 5.8). Subjects reported using an average of 4.4 g of cocaine per week (SD 3.3) for an average of 4.2 years. Sixty-eight (62 percent) reported predominantly freebase use of cocaine, 32 (29 percent) were intranasal users, and 10 (9 percent) were intravenous users. Thirty-three (30 percent) had some previous exposure to treatment. Forty-eight percent met DSM-III-R criteria for a lifetime diagnosis of alcohol dependence, 20 percent for a lifetime affective disorder, 13 percent for a lifetime anxiety disorder, 49 percent for antisocial personality disorder, and 65 percent for any other personality disorder. Analyses of variance and chi-square tests revealed there were no statistically significant differences by treatment group for any of these baseline variables.

Attrition

For subjects who initiated treatment (N = 121), the mean number of sessions completed was 7.2 (SD 3.6), and 49 subjects (40 percent) completed treatment (remained in treatment 12 weeks or completed 12 sessions). There were 4 subjects removed from the protocol due to clinical deterioration, 3 because of failure to comply with medication, 3 because of medication side effects (of these 10, 3 were in clinical management/desipramine, 4 in relapse prevention/desipramine, 2 in clinical management/placebo, and 1 in relapse prevention/placebo). There was one subject who became pregnant during treatment, one

subject who initiated AZT treatment, and four subjects who moved from the area. The remainder of early terminators were due to dropouts (N = 56).

The relapse prevention/desipramine group had the highest rate of subjects completing the full 12 weeks of treatment (49 percent), followed by comparable and lower rates in the clinical management/placebo, clinical management/desipramine, and relapse prevention/placebo groups (39 percent, 37 percent, and 36 percent, respectively, NS). By psychotherapy and medication type, subjects receiving relapse prevention were more likely to complete treatment than subjects receiving clinical management (57 percent versus 43 percent, NS), as were subjects who received desipramine as opposed to placebo (53 percent versus 47 percent, NS), although these differences were not statistically significant.

Outcome Analyses

Paired t-tests indicated that significant improvement occurred from pre- to posttreatment for all treatment groups. Significant effects for time were found across all treatment groups in frequency and quantity of cocaine use per week ($p < 0.001$), and for four of eight ASI domains (cocaine, alcohol, family/social, and psychological). As shown in table 1, no pre- to posttreatment changes were seen for medical, legal, and noncocaine drug use ASI composite scores, as pretreatment scores in each of these areas indicated low severity and were, therefore, unlikely to improve during treatment.

Table 1 presents means, standard deviations, and results of ANOVAs for primary (cocaine use) and secondary (ASI composite scores) outcome measures for the 110 subjects who completed at least two treatment sessions. There were no significant main effects for either psychotherapy or medication type, nor were there significant interactions between psychotherapy and medication.

To facilitate comparison with the authors' previous studies of desipramine with ambulatory cocaine abusers (Gawin et al. 1989), which reported significant decreases in cocaine use over 6 rather than 12 weeks of treatment as in the current study, the authors conducted repeated measures MANOVAs evaluating frequency and quantity of cocaine use per week during the first 6 weeks of treatment. There were significant

TABLE 1. *Treatment outcome: Cocaine use during treatment and pretreatment/ endpoint ASI composite scores by treatment group-Results of analysis of variance (N = 110).*

	Treatment Group[1]				
	CM/DMI N = 25	RP/DMI N = 29	CM/PLA N = 27	RP/PLA N = 29	SIG[2] of inter-action
Cocaine use during treatment					
Longest consecutive days of abstinence'	24.41±24.1	20.5±17.2	20.6±18.8	18.0±16.0	0.67
Percent abstinent days[4]	0.79±0.17	0.75±0.20	0.73±0.22	0.71±0.19	0.57
Percent cocaine-positive urines	0.33	0.33	0.27	0.39	0.18
ASI Composite Scores[5], mean ±SD					
Medical					
Pretreatment	0.17±0.28	0.19±0.25	0.11±0.19	0.16±0.27	
Endpoint	0.17±0.23	0.17±0.29	0.11±0.16	0.11±0.23	0.62
Employment					
Pretreatment	0.45±0.36	0.45±0.34	0.53±0.29	0.43±0.33	
Endpoint	0.51±0.37	0.41±0.30	0.59±0.26	0.38±0.30	0.06
Alcohol					
Pretreatment	0.11±0.14	0.14±0.19	0.08±0.09	0.12±0.15	
Endpoint	0.06±0.09	0.08±0.17	0.06±0.06	0.10±0.11	0.56**[6]
Cocaine'					
Pretreatment	0.70±0.18	0.69±0.17	0.71±0.18	0.61±0.16	
Endpoint	0.36±0.25	0.43±0.23	0.41±0.24	0.44±0.21	0.56**
Other drug					
Pretreatment	0.02±0.03	0.04±0.04	0.02±0.03	0.02±0.02	
Endpoint	0.01±0.02	0.03±0.04	0.02±0.03	0.02±0.02	0.07

TABLE 1. *Treatment outcome: Cocaine use during treatment and pretreatment/ endpoint ASI composite scores by treatment group—Results of analysis of variance (N = 110) (continued).*

	Treatment Group[1]				
	CM/DMI N = 25	RP/DMI N = 29	CM/PLA N = 27	RP/PLA N = 29	SIG[2] of inter-action
Legal					
Pretreatment	0.04±0.08	0.09±0.16	0.08±0.14	0.09±0.14	
Endpoint	0.09±0.17	0.06±0.12	0.05±0.13	0.06±0.11	0.68
Family/social					
Pretreatment	0.28±0.18	0.29±0.20	0.29±0.23	0.24±0.19	
Endpoint	0.16±0.17	0.27±0.23	0.20±0.21	0.15±0.15	0.12**
Psychological					
Pretreatment	0.19±0.16	0.27±0.23	0.20±0.22	0.16±0.16	
Endpoint	0.06±0.12	0.15±0.20	0.13±0.21	0.10±0.15	0.26**

[1]CM = clinical management; DMI = desipramine; RP = relapse revention; PLA = placebo.
[2]Results of 2x2 ANOVA, significance of F value. For primary outcome variables (consecutive days of abstinence during treatment, percent days abstinent, percent urines positive for cocaine) unadjusted group mean scores are presented. For ASI subscale composite scores, pretreatment scores reflect unadjusted means. Posttreatment scores reflect endpoint ratings for patients who were early terminators.
[3]Indicates duration of longest period of consecutive abstinence during treatment: Range 0 to 90.
[4]Indicates days of cocaine use as a percentage of total days in treatment.
[5]Range is 0 to 1; higher scores indicate higher problem severity.
"**Indicates significant ($p < 0.01$) effect for time by paired t-test.
[7]Indicates calculation of separate composite scores for cocaine versus other drug use.

desipramine effects ($F = 3.77$, p c 0.05) for grams of cocaine used per week, suggesting significant reduction in cocaine use for subjects treated with desipramine over placebo between treatment weeks 2 and 6. This

effect, however, was not significant beyond 6 weeks, which may be consistent with suggestions that desipramine treatment beyond 6 weeks counter-therapeutically cues relapse due to late onset cocaine-like stimulatory effects (Weiss 1988).

Severity by Treatment Interactions

Initial ANCOVAs indicated significant heterogeneity of regression for baseline severity of cocaine use on several primary outcome variables, suggesting the treatments worked differently at different levels of severity. Furthermore, two previous studies (Carroll et al. 1991a; Carroll et al. 1993a) suggested that severity was potentially an important predictor of treatment response in cocaine abusers. Therefore, to evaluate the relationship between baseline severity of cocaine use and treatment outcome, the sample was stratified into three levels: low (1 to 2.5 g of cocaine per week at baseline), moderate (2.6 to 4.4 g), and high severity (more than 4.5 g per week) in order to sharpen contrasts between low and high severity use. This classification of severity was associated with other indicators of severity such as frequency and chronicity of cocaine use and route of administration.

Exploratory 2x2x3 (medication by psychotherapy by severity) ANOVAs are presented in table 2, and the pattern of results is illustrated in figure 1. Significant severity by psychotherapy (relapse prevention versus clinical management) interactions indicated that higher severity subjects who received relapse prevention reported more consecutive days of abstinence, and lower severity subjects reported briefer periods of abstinence. The inverse was seen for clinical management; clinical management was associated with longer periods of abstinence for low-severity subjects and shorter periods of abstinence for high-severity subjects.

Similarly, analyses for treatment retention suggested significant severity by psychotherapy interactions. For relapse prevention, retention was better for higher severity patients, as low severity patients completed fewer total sessions (mean = 6.0), and higher severity patients completed more sessions (mean = 8.6) ($F = 3.6$, $p < 0.03$). For clinical management, there was better retention for low-severity patients (mean 8.0 sessions) than high-severity subjects (mean 6.1 sessions).

TABLE 2. *Interactions of treatment type with baseline level of severity of cocaine use results of three-way analysis of variance (N = 110).*

	TREATMENT				
	Psychotherapy		Pharmacotherapy		
	RP N = 52	CM N = 58	DMI N = 53	PLA[1] N = 57	Sig. of inter-action'
Percent treatment days abstinent					
Low severity'	0.78	0.82	0.79	0.80	
Moderate	0.83	0.77	0.82	0.79	
High	0.78	0.81	0.82	0.78	ns
Consecutive days abstinent[4]					
Low severity	16.6	33.1	27.8	18.8	
Moderate	22.1	25.2	23.2	24.0	Psych/sev
High	26.2	15.6	20.5	21.3	$p < 0.05$
Percent urine toxicology screens positive for cocaine					
Low severity	0.5 I	0.15	0.26	0.39	
Moderate	0.34	0.27	0.29	0.32	Psych/sev
High	0.28	0.47	0.42	0.30	$p < 0.01$
No. of treatment sessions completed[5]					
Low severity	6.0	8.0	6.4	7.2	
Moderate	8.1	6.8	8.1	6.9	Psych/sev
High	8.6	6.2	8.0	6.8	$p < 0.05$

NOTE: [1]RP = relapse prevention, CM = clinical management, DMI = desipramine, PLA = placebo. *Results of 2x2x3 ANOVA, significance of F. 'Indicates severity of baseline cocaine use: Low = 1 to 2.5 g/week, Moderate = 2.6 to 4.4 g/week, High = 4.5+ g /week. [4]Indicates duration of longest period of consecutive abstinence during treatment: Range: 0 to 90. 'Range: 1 to 12.

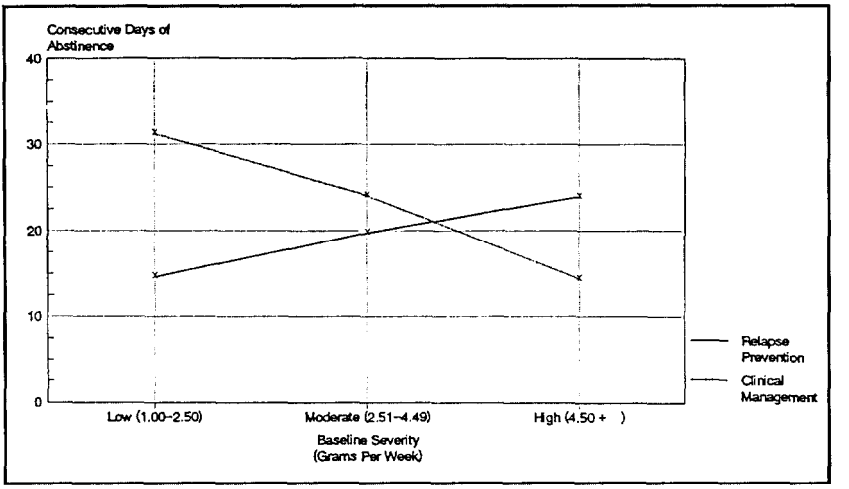

FIGURE 1. *Severity by psychotherapy interaction: Abstinence initiation in treatment (N = 110).*

There were no significant pharmacotherapy by severity interactions for treatment retention or reduction in cocaine use for the full sample. However, among the subsample of subjects who remained in treatment at least 5 weeks, greater efficacy of desipramine for low severity subjects was found on several cocaine outcomes.

Depression and Treatment Response

Given that the sample size might have precluded detection of all but the most robust psychotherapy-pharmacotherapy interactions, indications of enhanced effectiveness of pharmacotherapy through adding psychotherapy on an outcome where desipramine, a tricyclic antidepressant, might be expected to have a more robust effect, that is, in reduction of depressive symptoms, was then sought.

Thirty-seven percent of the sample was defined as having significant depressive symptomatology at baseline, using a cutoff of 8 on the Beck Depression Inventory (Beck and Beck 1972) and 6 or more on the Hamilton Depression Rating Scale (Hamilton 1960). Preliminary results indicate that desipramine appeared to be an effective antidepressant in this sample, in that depressed subjects treated with desipramine experienced a significant reduction in depressive symptoms compared to placebo-treated depressed subjects ($F = 4.0$, $p < 0.01$). However,

desipramine was not associated with significant improvements in cocaine use among either the depressed or euthymic subsamples. There were, however, consistent significant interactions for depression and psychotherapy, in that depressed subjects treated with relapse prevention remained in treatment significantly longer than depressed subjects treated with clinical management (9.7 versus 6.0 weeks, $F = 10.3$, $p < 0.01$) and maintained longer periods of consecutive abstinence during treatment (28.8 versus 20.2 days, $F = 28.8$, $p = 0.01$) (Carroll et al., in press).

CONCLUSIONS AND SUGGESTIONS FOR FUTURE RESEARCH

1. These findings suggest that overall, cocaine abusers benefited from treatment in significantly reducing their cocaine use from pretreatment levels. Moreover, improvements were not confined to cocaine abuse, but were seen for alcohol use, family and social interactions, and psychological functioning as well.

2. Although immediate posttreatment outcomes failed to demonstrate significant main effects for psychotherapy, pharmacotherapy, or their interaction, several design features also precluded unambiguous interpretation of the relative efficacy of psychotherapy versus pharmacotherapy in this sample. For example, all subjects receiving medication also received some form of psychotherapy; therefore, the efficacy of pharmacotherapy alone, without nonspecific effects of supportive clinical management or additional active ingredients of relapse prevention, could not be determined. Similarly, all subjects who received psychotherapy also received active or inert medication, which may have influenced their expectations for treatment effects.

   Several studies with depressed populations have failed to find meaningful differences in outcomes for psychotherapy alone versus psychotherapy plus placebo conditions (Frank and Kupfer 1992). However, cocaine abusers, through having repeatedly sought effects of psychoactive substances, may be more influenced by medication and expectancy effects than other populations. Therefore, comparisons of psychotherapy alone to psychotherapy/placebo combinations may be warranted.

3. Exploratory analyses revealed several patient-treatment interactions that might serve as guidelines for future patient-treatment matching

research, but which first require replication in other settings and samples. These included: (a) better outcomes for high severity cocaine users treated with cognitive-behavioral coping skills training than supportive clinical management replication, and better outcomes for low severity users treated with clinical management; (b) significant reduction in depressive symptoms for depressed cocaine abusers treated with desipramine over placebo; and (c) improved reductions in cocaine use for depressed cocaine abusers treated with relapse prevention over clinical management.

These findings are consistent with the state-trait model for cocaine treatment mentioned previously. Moreover, they underline the significance of heterogeneity among cocaine abusers, which will require development of specialized treatments for clinically distinct subgroups of cocaine abusers, rather than one simple pharmacologic or psychotherapeutic approach for all patients, For example, state aspects of cocaine dependence may indicate a need for specialized pharmacological adjuncts, such as antidepressant treatments for depressed cocaine abusers, disulfiram treatment for alcoholic cocaine abusers (Carroll et al. 1993b), methylphenidate treatment for cocaine abusers with residual attention deficit disorder (Khantzian et al. 1984), and so on. Similarly, while low-intensity psychotherapies may be sufficient for less severe cocaine abusers, specialized psychotherapies might be evaluated for cocaine abusers with distinct characteristics who would not be amenable to pharmacologic approaches. These might include motivational approaches (Miller and Rollnick 1991) for patients who are ambivalent around renouncing substance use, community reinforcement (Azrin 1976) or twelve-step (Nowinski et al. 1992) approaches for patients low in social supports and resources, cue extinction approaches (O'Brien et al. 1990) for those patients for whom continued conditioned craving for cocaine is problematic, and more directive cognitive behavioral approaches for higher severity and high psychopathology patients who have greater need for structure and support.

REFERENCES

Azrin, N.H. Improvements in the community-reinforcement approach to alcoholism. *Behav Res Ther* 14:39-48, 1976.

Beck, A.T., and Beck, R.W. Screening depressed patients in family practice: A rapid technique. *Postgrad Med* 52:81-85, 1972.

Carroll, K.M. Psychotherapeutic treatment of cocaine abuse: Models for its evaluation alone and in combination with pharmacotherapy. In: Tims, F.M., and Leukefeld, C.G., eds. *Cocaine Treatment: Research and Clinical Perspectives.* National Institute on Drug Abuse Research Monograph 135. DHHS Pub. No. (ADM) 93-3639. Washington, DC: Supt. of Docs., U.S. Govt. Print. Off., 1993.

Carroll, K.M.; Nich, C.; and Rounsaville, B.J. Differential symptom reduction in depressed cocaine abusers treated with psychotherapy and pharmacotherapy. *J Nerv Ment Dis,* in press.

Carroll, K.M.; Powers, M.D.; Bryant, K.J.; and Rounsaville, B.J. One-year follow-up status of treatment-seeking cocaine abusers: Psychopathology and dependence severity as predictors of outcome. *J Nerv Ment Dis* 181:71-79, 1993a.

Carroll, K.M.; Rounsaville, B.J.; and Gawin, F.H. A comparative trial of psychotherapies for ambulatory cocaine abusers: Relapse prevention and interpersonal psychotherapy. *Am J Drug Alcohol Abuse* 17:229-247, 1991a.

Carroll, K.M.; Rounsaville, B.J.; Gordon, L.T.; Nich, C.; Jatlow, P.M.; Bisighini, R.M.; and Gawin, F.H. Psychotherapy and pharmacotherapy for ambulatory cocaine abusers. *Arch Gen Psychiatry* 5 1: 177- 187, 1994a.

Carroll, K.M.; Rounsaville, B.J.; and Keller, D.S. Relapse prevention strategies in the treatment of cocaine abuse. *Am J Drug Alcohol Abuse* 17:249-265, 1991b.

Carroll, K.M.; Rounsaville, B.J.; and Nich, C. Blind man's bluff'? The effectiveness and significance of psychotherapy and pharmacotherapy blinding procedures in a randomized clinical trial. *J Consult Clin Psychol* 62:276-280, 1994b.

Carroll, K.M.; Ziedonis, D.; O'Malley, S.S.; McCance-Katz, E.; Gordon, L.; and Rounsaville, B.J. Pharmacologic interventions for abusers of alcohol and cocaine: A pilot study of disulfiram versus naltrexone. *Am J Addict* 2:77-79, 1993b.

Extein, I., and Bowers, M.B. State and trait in psychiatric practice *Am J Psychiatry* 136:690-693, 1979.

Fawcett, J.; Epstein, P.; Fiester, S.J.; Elkin, I.; and Autry, J.H. Clinical management-imipramine/placebo administration manual: NIMH Treatment of Depression Collaborative Research Program. *Psychopharmacol Bull* 23:309-324, 1987.

Frank, E., and Kupfer, D.J. Does a placebo tablet affect psychotherapeutic treatment outcome? Results from the Pittsburgh study of maintenance therapies in recurrent depression. *Psychother Res* 2:102-111, 1992.

Gawin, F.H.; Kleber, H.D.; Byck, R.; Rounsaville, B.J.; Kosten, T.R.; Jatlow, P.I.; and Morgan, C.B. Desipramine facilitation of initial cocaine abstinence. *Arch Gen Psychiatry* 46: 117-121, 1989.

Hamilton, M. A rating scale for depression. *J Neurol Neurosurg Psychiatry* 23:56-62, 1960.

Higgins, S.T.; Budney, A.J.; Bickel, W.K.; and Hughes, J.R. Achieving cocaine abstinence with a behavioral approach. *Am J Psychiatry* 150:763-769, 1993.

Hill, C.E.; O'Grady, K.E.; and Elkin, I. Applying the Collaborative Study Psychotherapy Rating Scale to rate therapist adherence in cognitive-behavior therapy, interpersonal therapy, and clinical management. *J Consult Clin Psychol* 60:73-79, 1992.

Kang, S.Y.; Kleinman, P.H.; Woody, G.E.; Millman, R.B.; Todd, T.C.; Kemp, J.; and Lipton, D.S. Outcomes for cocaine abusers after once-a-week psychosocial therapy. *Am J Psychiatry* 148:630-635, 1991.

Khantzian, E.J.; Gawin, F.I.; and Kleber, H.D. Methylphenidate treatment of cocaine dependence: A preliminary report. *J Subst Abuse Treat* 1:107-112, 1984.

Klerman, G.L. Combining drugs and psychotherapy in the treatment of depression. In: Greenblatt, M., ed. *Drugs in Combination with Other Therapies.* New York: Grune and Stratton, 1975.

Levin, F.R., and Lehman, A.F. Meta-analysis of desipramine as an adjunct in the treatment of cocaine addiction. *J Clin Psychopharmacol* 11:374-378, 1991.

Marlatt, G.A., and Gordon, J.R., eds. *Relapse Prevention: Maintenance Strategies in the Treatment of Addictive Behaviors.* New York: Guilford, 1985.

McLellan, A.T.; Luborsky, L.; Woody, G.E.; and O'Brien, C.P. An improved diagnostic evaluation instrument for substance abuse patients: The Addiction Severity Index. *J Nerv Ment Dis* 168:26-33, 1980.

Miller, W.R., and Rollnick, S. *Motivational Interviewing: Preparing People to Change Addictive Behavior.* New York: Guilford, 1991.

Nowinski, J.; Baker, S.; and Carroll, K.M.. *Twelve-step facilitation therapy manual: A clinical research guide for therapists treating individuals with alcohol abuse and dependence.* NIAAA Project MATCH Monograph Series Volume 1. DHHS Publication No. (ADM)92-1893. Rockville, MD: National Institute on Alcohol Abuse and Alcoholism, 1992.

O'Brien, C.P.; Childress, A.R.; McLellan, A.T.; and Ehrman, R. Integrating systematic cue exposure with standard treatment in recovering drug dependent patients. *Addict Behav* 15:355-365, 1990.

Rounsaville, B.J.; O'Malley, S.; Foley, S.; and Weissman, M.M. Role of manual-guided training in the conduct and efficacy of interpersonal psychotherapy for depression. *J Consult Clin Psychol* 56:681-688, 1988.

Weiss, R.D. Relapse to cocaine abuse after initiating desipramine treatments. *JAMA* 260:2545-2546, 1988.

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Can Psychotherapy Rescue Naltrexone Treatment of Opioid Addiction?

Bruce J. Rounsaville

NALTREXONE'S PROMISE

Naltrexone pharmacotherapy for opioid addiction is, on paper, an almost perfect treatment. To start with, it has a clear mechanism of action and a compelling rationale. It selectively competes for opioid receptors and prevents addicts from achieving reinforcement from continued opioid use and from resuming physical dependence if they do use illicit opioids. From a learning theory perspective, the conditioned linkage between use of opioids and positive reinforcement should be extinguished over time as the addict either refrains from further opioid use or obtains no psychoactive effect from continued use. It is orally active, exquisitely powerful (affinity for opioid receptors being 20 times that of morphine), and can be dispensed on a three times/weekly schedule if monitored dispensing is required. Alternatively, because it is not psychoactive, diversion is not an issue, and patients or significant others can administer the medication on an outpatient basis. The side-effect profile, at least on the recommended dose of 50 mg per day, is generally benign, although 5 to 10 percent of detoxified opioid addicts experience immediate, intolerable levels of withdrawal-like effects including agitation, anxiety, insomnia, light-headedness, sweating, dysphoria, and nausea. Most patients on naltrexone experience few or no symptoms after the first 1 to 2 weeks of treatment; for a substantial minority (20 to 30 percent) protracted discomfort is experienced. The only really serious potential side effect is hepatotoxicity (Maggio et al. 1985), but this has only been shown to be a problem when daily dosage levels are six times the normal dose. A serious inconvenience, although one that should only rarely be an issue, is that patients on naltrexone are unresponsive to ordinary dosages of opioid analgesics when these are legitimately administered for control of pain.

To put naltrexone's seeming excellence in perspective, one can evaluate the pharmacotherapeutic agents available for treatment of other drugs of abuse, such as alcohol, cocaine, stimulants, sedatives, or marijuana.

While alcohol can be treated with disulfiram, an aversive agent, selective antagonists or aversive agents have not been developed for other classes of drugs. In fact, searching for and testing of antagonist agents is a prominent strategy in the process of developing pharmacotherapies for cocaine and alcohol (Meyer 1989). This process is likely to be less straightforward and less successful than in the case of opioids, as psychoactive effects of alcohol and of cocaine do not appear to be associated as clearly with a single type of central nervous system receptor. Hence, development of an antagonist that is even nearly as good as naltrexone for other substances would be a pharmacological breakthrough. However, the optimism for the utility of alcohol or cocaine antagonists should be reconsidered in light of the clinical experience with naltrexone, a more specific and theoretically perfect opioid antagonist.

NALTREXONE'S UNFULFILLED PROMISE

Despite naltrexone's great promise, its impact on the practical management of opioid addiction in the United States has been vanishingly small since its introduction to the market in 1986. Data on sales from naltrexone's sole manufacturer have indicated that only around 9,000 to 12,000 prescriptions per year were filled for naltrexone between 1986 and 1992 (R. Croop, personal communication, July 1993). Given that official estimates of the number of opioid addicts in the United States are around 600,000, and that around 150,000 are in treatment at any given time, it is clear that naltrexone has been used for only a small percentage (i.e., 1 to 3 percent) of treated opioid addicts. Outside of academic and research settings where original efficacy and safety studies were conducted, naltrexone treatment is virtually unknown. Even at the Substance Abuse Treatment Unit site in New Haven, which has utilized naltrexone since the early 1970s the census for the Substance Abuse Treatment Unit naltrexone maintenance program is 50 to 60 clients, while the methadone maintenance programs treat around 600 patients.

Parallel to naltrexone's limited impact in the treatment community, research on naltrexone for opioid addicts has been at a virtual standstill for the past decade. A literature review for a presentation on psychosocial interventions and naltrexone showed that all of the published reports are from the early 1980s and before. Only two recently funded National Institute on Drug Abuse clinical trials have addressed naltrexone: a study by McLellan and colleagues (McLellan et al.,

personal communication, June 1993) evaluating naltrexone treatment linked to parole and one by Wesson and colleagues (Wesson et al., personal communication, May 1993) evaluating different naltrexone induction strategies aimed at reducing initial dropout.

Even the initial phase of research on naltrexone for opioid addicts generated only a handful of trials evaluating the impact of psychotherapy or behavioral interventions, and, as shown below, many of these were open or nonrandomized or both. The evaluations of naltrexone treatment typically are focused on two phases: (1) initial stabilization, consisting of the first 6 to 8 weeks of treatment, during which time prolonged withdrawal symptoms and social supports are the key issues, and (2) maintenance, when initial pharmacological issues are resolved and treatment is aimed at rehabilitation.

STABILIZATION TRIALS

Several behavior modification approaches have been used during stabilization. The project by Callahan (1980) and Martin and colleagues (1973) reported that 21 percent completed 6 weeks on naltrexone alone, while 49 percent completed 6 weeks with behavior therapy plus naltrexone. The difference did not achieve significance because of the small numbers. Their treatment included contingency contracting and behavioral techniques such as thought stopping. Contingency payment is another technique that has been employed with addicts. In a nonrandomized study by Meyer and colleagues (1976, 1979, pp. 215-230), addicts were paid $1.00 a day to consume naltrexone. The paid addicts had a 72 percent success rate at 1 month compared to nonpaid addicts, who had only a 25 percent success rate, a difference significant at the .02 level. However, this followed a 2-month inpatient stay. Another study of contingency payment by Grabowski (1979) showed an 89 percent success rate at both 1 and 2 months in the paid addicts, while previous addicts who had received a similar amount of money (about $40 a month) without this contingency program had only a 60 percent success rate at 1 month and a 40 percent success rate at 2 months. Judson and Goldstein (1979) studied a group of 73 postlevomethadyl acetate (LAAM) patients compared to 46 street addicts. The LAAM patients had been extensively educated about naltrexone with handouts, discussion, and even a quiz over a period of months. In spite of this, the group did no better than the street group. Average retention initially was 6 to 7 weeks. By 1 month, approximately half of the patients had dropped out;

by 5 months only about 10 percent remained. Dose (60 mg versus 120 mg) did not have a significant effect on treatment duration.

Nonbehavioral therapies also have been tested. Resnick and colleagues (1981) followed 37 addicts who had been randomly assigned to individual counseling or no counseling. At 1 month, 77 percent (17/22) were still in treatment in the counseling group, while only 33 percent (5/15) were still in treatment in the noncounseling group. The difference was significant at the .01 level. When the addicts were stratified by street versus postmethadone, overall program retention was significantly better for the street addicts with counseling, but not for the postmethadone addicts. Thus, as during the induction phase, street addicts seem to benefit from individual counseling and show improved program retention. In a nonrandomized study of multiple family therapy at Yale University, Anton and colleagues (1981) demonstrated that during the first month of naltrexone therapy, addicts in family therapy had a very low dropout-92 percent retention-significant at the .001 level. This suggests that family therapy also may be of benefit to addicts during this stabilization phase.

MAINTENANCE TRIALS

The project by Callahan (1980) and Martin and colleagues (1973) also reported that behavior therapy lengthened time on naltrexone from an average of 44 days up to 85 days, significant at the .02 level (Callahan 1976, pp. 150-157). A later paper from this program indicated that the behavior therapy group had less drug use and better program retention from 0 to 7 months, but no differences were evident at 8 to 14 months or 15 to 21 months (Callahan 1980). Together, these findings suggest that contingency payment and behavior modification only delay the initial dropout from a naltrexone program. Data from Resnick and colleagues (1981) showed that the difference between the counseling groups was smaller at 3-month and 6-month points than after the stabilization phase. For addicts opiate-free at 3 months, the percentages were 54 percent (counseling) versus 40 percent. Similar trends were evident for the percentage of ex-addicts taking naltrexone; at 3 months the percentages were 27 percent (6/22) (counseling) versus 0 percent (0/15), and at 6 months the percentages were 9 percent (2/22) versus 0 percent. In a broader context, behavioral treatments improve compliance with naltrexone, and naltrexone ingestion enables the counselor to establish a

therapeutic relationship within which lifestyle changes can be discussed and made.

Figure 1 illustrates the pattern of dropout from naltrexone treatment for behavior modification (BM) from Callahan's program (1980) and individual counseling (IC) from the program of Resnick and colleagues (1981). By 3 to 4 months, these two treatments showed no difference in the percentage of addicts remaining on naltrexone compared to the control group of addicts. The control group curve is a composite of the three studies illustrated with the standard error given for each month. Figure 1 also compares the results for multiple family therapy (MFT) to these other two treatments. For any month the percentage of addicts who remained on naltrexone and drug-free was larger in the MFT group than the percentage of addicts in the other two treatments or in the control group.

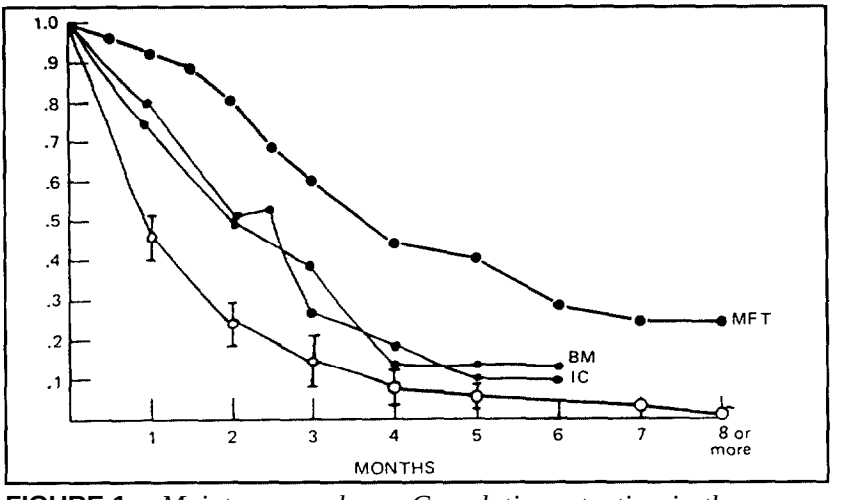

FIGURE 1. *Maintenance phase: Cumulative retention in three programs (●) compared to addicts maintained on naltrexone alone (○).*

KEY: MFT = multiple family therapy (Anton et al. 1981)
BM = behavior modification (Callahan 1976)
IC = individual counseling (Resnick et al. 1981)

WHY IS NALTREXONE'S PROMISE UNFULFILLED?

While figure 1 illustrates the initial superiority of combined psychosocial approaches to naltrexone alone and the more enduring promise of a family therapy approach, it is hardly encouraging regarding the overall 6-month dropout rate of 70 percent or more for even the most successful group of comparatively unselected addicts. Moreover, most of these early dropouts return to illicit opioid use. These discouraging findings are further compounded by survey results from treatment-seeking opioid addicts showing that only 10 to 15 percent are willing to attempt treatment with a drug that "keeps you from getting high" (Greenstein et al. 1984).

A major factor in naltrexone's limited role is that a powerful alternative pharmacotherapy, methadone, already was available when naltrexone was introduced. Compared with naltrexone, methadone has many key advantages. First, there is no required detoxification phase. Hence, there is no initial discomfort in taking methadone. Moreover, with methadone there are no protracted withdrawal symptoms, which frequently endure throughout the first 2 to 6 weeks on naltrexone. Second, methadone provides a mild opioid "high" and does not preclude the use of illicit opioids to boost this effect. Third, abrupt withdrawal of methadone treatment results in a protracted and often severe opioid withdrawal syndrome. Hence, addicts have powerful positive incentives to initiate methadone treatment and negative consequences for premature dropout. These advantages result in retention rates on methadone maintenance that are the mirror image of those on naltrexone, with 50 to 90 percent of patients remaining in treatment for 6 months or more (Lowinson et al. 1992, pp. 550-561).

In a free-choice situation, only a small minority of opioid addicts will initially choose naltrexone, and most of these will drop out before achieving a stable, opioid-free lifestyle. Thus, these factors explain the very limited place of naltrexone maintenance treatment.

CAN PSYCHOTHERAPY SAVE NALTREXONE?

Before addressing this issue, it may be well to ask if naltrexone should be saved or, rather, be more widely used in place of methadone or of drug-free approaches. This author would argue that naltrexone is underutilized.

Compared with methadone, naltrexone has many potential advantages. First, because it is nonaddicting, it can be used in a variety of nonspecialized settings such as medical clinics, and it can be prescribed without concerns about diversion. Second, the cost of naltrexone treatment, in terms of demands on professional time and of patient time, are much smaller than those associated with methadone maintenance requiring daily or near-daily clinic visits. Third, the chances for success after an adequate course of treatment are enhanced on naltrexone, as protracted withdrawal already has been handled during the initial phase of naltrexone treatment. In contrast, detoxification and postdetoxification are periods of great vulnerability for relapse in methadone-maintained patients because of the need for lengthy detoxification and of protracted withdrawal symptoms. In fact, methadone maintenance may make addicts more physically dependent on opioids than they were prior to treatment, as the typical street addict can only obtain an intermittent supply of opioids of varying strengths. Fourth, from a behavioral perspective, the course of naltrexone treatment has allowed the patient to decondition the connection between cues of everyday life and the experience of opioid intoxication. This is likely to enhance an addict's ability to avoid cue-induced craving and relapse following medication discontinuation. In contrast, the course of methadone maintenance is characterized by continuing to go through the day in a medicated state. Fifth, naltrexone is neither associated with continued potential reinforcement from heroin use nor with potential synergistic effects from cocaine use. Hence, addicts are less likely to continue intravenous drug abuse while on naltrexone than on methadone, thereby reducing potential spread of human immunodeficiency virus (HIV) and other needle-borne diseases. Of course, none of these potential advantages of naltrexone can be realized unless patients are inducted and retained in treatment.

The situation of naltrexone and psychotherapy for opioid addicts is one in which neither treatment is likely to be effective alone, and a combined approach is essential. As noted earlier, in the review of available trials, naltrexone offered without a psychosocial intervention is largely ineffective, and studies of ambulatory psychotherapy for opioid addicts offered outside of methadone maintenance likewise were plagued by unacceptably high dropout rates (O'Malley et al. 1972). This contrasts with models for potential interaction between pharmacotherapy and psychotherapy of other psychiatric disorders such as depression, in which both treatments have been shown to be effective alone (Elkin et al. 1988a, 19886; Weissman 1979).

If psychotherapy or behavioral interventions are to enhance the efficacy of naltrexone treatment, they must be tailored to address naltrexone's weaknesses, particularly its weaknesses in comparison to its strongest competitor, methadone.

The first weakness to address is naltrexone's lack of immediate positive pharmacological reinforcement. To address this issue, provision of positive incentives for initiation of and maintenance on naltrexone treatment is needed. In fact, simple payment of a small fee improved initial compliance in several early studies (Callahan 1980; Grabowski 1979; Martin et al. 1973; Meyer et al. 1976; Meyer et al. 1979, pp. 215-230). Given that the major alternative to naltrexone treatment is methadone, the provision of positive incentives could take the form of more favorable conditions in contrast to methadone (e.g., shorter waiting list, more privileges, lower fees). In addicted physicians (Tennant et al. 1984; Washton et al. 1984), a group for whom naltrexone has been shown to have great promise, the relative lack of pharmacological reinforcement of naltrexone is outweighed by the inconvenience and public nature of methadone maintenance.

The second weakness for naltrexone is that there are no pharmacological negative reinforcements for premature dropout. Whereas abrupt cessation of methadone leads to serious withdrawal, naltrexone can be discontinued easily. This weakness could be addressed with contingency contracting, possibly involving family members as participants, in which negative consequences are linked to premature dropout.

A third key weakness for naltrexone is the initial presence of aversive naltrexone side effects and protracted withdrawal symptoms. While this issue has been addressed by inpatient initiation and by pharmacological strategies, psychosocial interventions such as provision of added support, involvement of the addicts' social network, and preparedness training could be added. The presence of a major aversive consequence for naltrexone discontinuation (i.e., return to incarceration) is the likely reason for naltrexone's success with parole and probation groups (Brahen et al. 1984).

TECHNICAL CONSIDERATIONS IN NALTREXONE VERSUS METHADONE RESEARCH DESIGNS

Because methadone maintenance is the major, more successful alternative to naltrexone treatment, it is the optimal comparison condition for systematic efficacy trials that combine psychosocial interventions with naltrexone. It is noteworthy that this kind of systematic, randomized comparison of naltrexone to methadone maintenance has not been reported in the published literature. It is likely that problems with subject recruitment in a noncoercive situation have made such direct comparisons unfeasible. In the section below, a number of potential interventions that may enhance naltrexone's efficacy are described. For these to have an impact on treatment approaches that are actually used, rigorous demonstration of efficacy will be required. Such studies will need to include design features that address special problems inherent in a naltrexone versus methadone design.

First, the central problem in a naltrexone versus methadone study is unfeasibility of noncoercive recruitment. Because methadone is the standard treatment and is generally more initially acceptable, opioid addicts seeking treatment have little incentive to enter a research protocol in which they have a 50 percent chance of receiving naltrexone. To manage this issue, one strategy would involve making naltrexone treatment the standard initial approach for targeted subgroups of opioid addicts such as those with no prior methadone experience, those under legal pressure, or those with good prognostic features (e.g., employed, good social supports). In a program with this approach, subjects might be recruited more readily if they knew that they had a 50 percent chance of receiving methadone instead of naltrexone. A drawback to this approach is that clients may opt to enter alternative methadone programs in the same geographical area rather than seeking treatment with naltrexone, a problem that undermined the well-known therapeutic community versus methadone trial attempted by Bale and colleagues (1980). Other incentives for participation in such a trial might involve avoidance of a waiting list for methadone, low-cost treatment or provision of other desirable incentives such as those involved in a community reinforcement approach (Higgins et al. 1993).

A second potential problem in research on naltrexone versus methadone is a potentially high dropout rate and differential dropout. Naltrexone and methadone are likely to appeal to different kinds of patients. Moreover, this author suggests that naltrexone would require some sort of

added psychosocial treatment (e.g., couple's treatment) in order to counter the early attrition problems seen in the past. Some of the problems arising from high attrition or differential attrition can be dealt with in the data-analysis phase. For example, endpoint analysis can be used, including all subjects in the efficacy analysis by using their clinical status at the time of attrition as the outcome rating (Fleiss 1986). Alternatively, analysis can be performed on an "intention to treat" sample at a standard time point regardless of the actual treatment the subject received following dropout from initially assigned treatment (Lavori 1992). However, all of the data-analytic strategies for managing differential attrition involve assumptions that may be incorrect and are less satisfactory than those that prevent the problem in the first place. This is best accomplished in the recruitment phase of the study by ensuring that subjects entered are equally willing and able to become engaged in the alternative approaches. For example, if a design involves randomization to a spouse-assisted versus individual approach, it is crucial that subjects randomized to both conditions have spouses who are willing to participate in treatment. Demonstration of this potential for spouse involvement could involve a requirement that the spouse participate in pretreatment assessments.

A third consideration in designing naltrexone versus methadone studies is the need to include outcome measures that are the most likely to tap the likely strengths and weaknesses of the two treatments. Some of these potential differences can be readily assessed in the course of a relatively brief trial. For example, methadone is likely to be superior in terms of attrition at 1 to 2 months, while naltrexone is likely to be superior in terms of opioid-free urine specimens. However, the likely benefits of naltrexone may not be noted with standard outcome measures or with outcome measures evaluated in the long term. Naltrexone's two major areas of superiority are likely to be in cost-benefit and in long-term abstinence from opioids. Because naltrexone does not involve daily dosing, even in the initial phases of treatment, treatment may be less expensive, both in terms of personnel costs and in terms of clients' loss of leisure or occupational time. Hence, detailed assessments and calculation of total social and treatment costs and benefits of the two approaches would be required to provide an optimal comparison. The greatest potential area of superiority of naltrexone is at treatment termination, with the lack of withdrawal symptoms easing the transition from treatment to a drug-free state. Hence, a study comparing naltrexone to methadone would necessitate a long-term, posttreatment followup. To be practicable, such a study would require what many would see as

premature and arbitrary cessation of the comparison methadone treatment (e.g., after 6 to 12 months of maintenance). Another potential difference in outcome of naltrexone versus methadone is in long-term success of early dropouts. An argument against initiating first-time treatment seekers on naltrexone is that those who drop out early may become discouraged about all treatment and fail to obtain alternative treatment that might be more acceptable. Conversely, methadone's high retention is seen as a major strength, especially if early dropout is associated with exposure to such dangers as needle-borne infections like HIV. To evaluate such an issue, it is critical that investigators devote considerable efforts to follow up not only treatment completers but also all early dropouts.

PSYCHOTHERAPY AND NALTREXONE COMBINATIONS-WHAT MIGHT WORK?

In this section, the general strategy of tailoring behavioral treatments to naltrexone's weaknesses will be elaborated and further explored in terms of potential program designs.

Naltrexone as First-Line Treatment

One general strategy for enhancing acceptance and utilization of naltrexone would require changes at the treatment organization level. This would be a programmatic decision to require an initial course of naltrexone treatment as a prerequisite for initiation of methadone maintenance. This program revision would address naltrexone's weakness of having low initial attractiveness. Addicts with prior methadone maintenance experience have been reported to have higher dropout rates than those for whom naltrexone is the initial treatment (Resnick et al. 1979). The main rationale for offering naltrexone as the first-line treatment is that even if it is effective only with a minority, it may save that group from the expense and disadvantages of methadone maintenance mentioned earlier. More and more, methadone maintenance is seen as a treatment of indefinite duration. Hence, before initiating a treatment that may last for many years, use of an opioid-free treatment may be highly desirable. However, this kind of programmatic commitment to naltrexone has been the exception and not the rule. From a research perspective, this kind of prior decision would be required to deal with recruitment issues in a clinical trial contrasting naltrexone to methadone maintenance as an initial treatment.

Negative Reinforcements for Discontinuation or Contingency Contracting

To address the problem that naltrexone is comparatively easy to discontinue (there are no withdrawal symptoms), it could be offered in the context of a contract that would call for negative contingencies for discontinuation. Such an approach has been reported as successful with addicted physicians for whom the alternative to treatment is losing their medical license (Tennant et al. 1984; Washton et al. 1984). While this group constitutes only a small fraction of opioid addicts, contingency contracting could be more broadly used with addicts under legal pressure, where the alternative to treatment is violation of parole or probation. While this approach has promise for the duration of the parole or probation, experience with contingency contracting with cocaine abusers suggests that continued avoidance of illicit drug use is likely to cease with the expiration of the contract (Anker and Crowley 1982).

Increase Positive Incentives With Naltrexone

As noted above, early attrition from naltrexone has been substantially reduced by providing basic positive incentives such as monetary payments for taking the medication. This initial superiority in retention, however, did not endure after several months. An approach that could build on this finding would be to adapt the Community Reinforcement Approach (CRA) to naltrexone maintenance. This is a multifaceted program that combines cognitively oriented coping skills training, provision of positive behavioral reinforcements for drug-free urine specimens, and significant-other involvement in treatment (Azrin et al. 1973, pp. 952-959). Higgins and colleagues (1991, 1993) have reported substantial benefits from this approach in ambulatory cocaine abusers, demonstrating its superiority over standard treatment and the effectiveness of individual program components including involvement of the significant others and inclusion of a voucher system to reward drug-free urine specimens. Adapting such a program to naltrexone could deal with the early dropout issues by providing vouchers for taking medication or for drug-free urine specimens. By using this early phase to engage not only the addict but a significant other, the program is likely to have an enhanced probability of long-term retention, such as that shown by Anton and colleagues (1981) with naltrexone patients offered a family therapy intervention. Provision of vouchers and of the social support from a significant other also may counterbalance the discomfort experienced by many opioid addicts during the initial naltrexone

induction phase. The willingness to endure mild withdrawal symptoms during this time may be increased if other incentives are in effect.

CONCLUSIONS

Despite its many advantages over methadone maintenance, naltrexone treatment is underutilized because of several key weaknesses relative to methadone: it provides no opioid agonist effects, it is associated with initial aversive side effects in a substantial number of clients, and it is easy to discontinue because it lacks withdrawal effects, To maximize its potential, naltrexone should be offered in the context of a program of psychosocial interventions that address its key weaknesses. Potential strategies could include offering of naltrexone as the first-line treatment, contingency contracting to provide negative reinforcement for treatment discontinuation, or use of a community reinforcement approach to provide a range of positive incentives for recruitment and retention on naltrexone. Such strategies are conducive to empirical testing, but systematic efficacy studies would need to include design features that have not been utilized in prior research on naltrexone treatment.

REFERENCES

Anker, A.A., and Crowley T.J. Use of contingency contracts in specialty clinics for cocaine abuse. In: Harris, L.S., ed. *Problems of Drug Dependence 1981.* National Institute on Drug Abuse Research Monograph 41. DHHS Pub. No. (ADM)82-190760. Washington, DC: Supt. of Docs., U.S. Govt. Print. Off., 1982.

Anton, R.F.; Hogan, I.; Jalai, B.; Riordan, C.E.; and Kleber, H.D. Multiple family therapy and naltrexone in the treatment of opiate dependence. *Drug Alcohol Depend* 8:157-168, 1981.

Azrin, N.H.; Naster, B.J.; and Jones, R. Reciprocity counseling: A rapid learning based procedure for marital counseling. *Behav Res Ther* 11:364-382, 1973.

Bale, R.N.; Van Stone, W.W.; Kaldan, J.M.; Engelsing, T.M.J.; Elashiff, R.M.; and Zarcone, V.P. Therapeutic communities vs. methadone maintenance: A prospective controlled study of narcotic addiction treatment: Design and one year follow-up results. *Arch Gen Psychiatry* 37:179-193, 1980.

Brahen, L.S.; Henderson, R.K.; Capone, T.; and Kordal, N. Naltrexone treatment in a jail work-release program. *J Clin Psychiatry* 45:49-52, 1984.

Callahan, E.J. Comparison of two naltrexone treatment programs: Naltrexone alone versus naltrexone plus behavior therapy. In: Julius, D., and Renault, P., eds. *Narcotic Antagonists: Nultrexone.* National Institute on Drug Abuse Research Monograph 9. NTIS PB #255-833/AS. Washington, DC: Supt. of Docs., U.S. Govt. Print. Off., 1976.

Callahan, E.J. The treatment of heroin addiction: Naltrexone alone with behavior therapy. *Am J Drug Alcohol Abuse* 7:795-807, 1980.

Elkin, I.; Pilkonis, P.A.; Docherty, J.P.; and Sotsky, S.M. Conceptual and methodological issues in comparative studies of psychotherapy: I. Active ingredients and mechanisms of change. *Am J Psychiatry* 145:909-917, 1988a.

Elkin, I.; Pilkonis, P.A.; Docherty, J.P.; and Sotsky, S.M. Conceptual and methodological issues in comparative studies of psychotherapy: II. Nature and timing of treatment effects. *Am J Psychiatry* 145:1070-1076, 19886.

Fleiss, J.L. *The Design and Analysis of Clinical Experiments.* New York: John Wiley & Sons, Inc., 1986.

Grabowski, J. Effects of contingent payment on compliance with a naltrexone regimen. *Am J Drug Alcohol Abuse* 6(3):355-365, 1979.

Greenstein, R.A.; Amdt, J.C.; McClellan, A.T.; O'Brien, C.P.; and Evans, B. Naltrexone: A clinical perspective. *J Clin Psychiatry* 45:25-28, 1984.

Higgins, ST.; Budney, A.L.; Bickel, W.K.; Hughes, L.; Florian, F.; and Gary, B. Achieving cocaine abstinence with a behavioral approach. *Am J Psychiatry* 150:763-769, 1993.

Higgins, S.T.; Delaney, D.D.; Budney, A.J.; Bickel, W.K.; Hughes, J.R.; Foerg, F.; and Fenwick, J.W. A behavioral approach to achieving initial cocaine abstinence. *Am J Psychiatry* 148:1218-1224, 1991.

Judson, B.A., and Goldstein, A. Rapid induction to stable dosages of levomethadyl acetate (LAAM). *Drug Alcohol Depend* 4:461, 1979.

Lavori, P.W. Clinical trials in psychiatry: Should protocol deviation censor patient data? *Neuropsychophurmucology* 6:39-63, 1992.

Lowinson, J.H.; Marion, I.H.; Joseph, H.; and Dole, V.P. Methadone maintenance. In: Lowinson, J.H.; Ruiz, P.; Millman, R.B.; and Langrod, J.G. eds. *Substance Abuse: A Comprehensive Textbook.* Baltimore: Williams and Wilkins. 1992.

Maggio, C.A.; Presta, E.; and Bracco, E.F. Naltrexone and human eating behavior: A dose-ranging inpatient trial in moderately obese men. *Bruin Res Bull* 14:657-661, 1985.

Martin, W.R.; Jasinski, D.; and Mansky, P. Naltrexone, an antagonist for the treatment of heroin dependence. *Arch Gen Psychiatry* 23:784-789, 1973.

Meyer, R.E. Prospects for a rational pharmacotherapy of alcoholism. *J Clin Psychiatry* 50:403-412, 1989.

Meyer, R.E.; Mirin, S.M.; Altman, J.L; and McNamer, B. A behavioral paradigm for the evaluation of narcotic antagonists. *Arch Gen Psychiatry* 33:371-377, 1976.

Meyer, R.E.; Mirin, S.M.; and Zackow, F. Community outcome on narcotic antagonists. In: Meyer, R.E., and Mirin, S.M., eds. *The Heroin Stimulus.* New York: Plenum Press, 1979.

O'Malley, J.E.; Anderson, W.H.; and Lazare, A. Failure of outpatient treatment of drug abuse: I. Heroin. *Am J Psychiatry* 128:865-868, 1972.

Resnick, R.; Schuyten-Resnick, E.; and Washton, A.M. Narcotic antagonists in the treatment of opioid dependence: Review and commentary. *Compr Psychiatry* 20:116-125, 1979.

Resnick, R.B.; Washton, A.M.; Stone-Washington, N.; and Rawson, R.A. "Psychotherapy and Naltrexone in Opioid Dependence." Paper presented at Committee on Problems of Drug Dependence, San Francisco, CA, July 13, 1981.

Tennant, F.S.; Rawson, R.A.; Cohen, A.J.; and Mann, A. Clinical experience with naltrexone in suburban opioid addicts. *J Clin Psychiatry* 45:41-45, 1984.

Washton, A.M.; Pottash, A.C.; and Gold, M.S. Naltrexone in addicted business executives and physicians. *J Clin Psychiatry* 45:39-41, 1984.

Weissman, M.M. The psychological treatment of depression: Evidence for the efficacy alone, in comparison with and in combination with pharmacotherapy. *Arch Gen Psychiatry* 36: 1261-1266, 1979.

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Strategies To Maximize the Efficacy of Naltrexone for Alcohol Dependence

Stephanie S. O'Malley

Psychosocial treatments for alcoholism have been shown to increase abstinence rates and improve the quality of life for many alcoholics (Miller and Hester 1986, pp. 121-174). Nonetheless, a significant proportion of alcoholics find it difficult to maintain initial treatment gains and eventually relapse to problematic drinking. In an effort to reduce relapse rates, there has been considerable interest in developing pharmacological treatments that can be incorporated into psychosocial treatment approaches (Litten and Allen 1991). One pharmacological agent that currently is receiving increased attention is naltrexone, an opioid antagonist. The potential value of naltrexone was initially suggested by extensive research using animal models, which demonstrated that opioid antagonists can reduce alcohol drinking under a variety of conditions. (For a review, see Froelich and Li 1993.) Subsequently, two controlled clinical trials have been conducted that provide evidence for the efficacy of opioid antagonists in the treatment of alcohol dependence (Volpicelli et al. 1992; O'Malley et al. 1992).

Volpicelli and his colleagues first evaluated the potential value of naltrexone as adjunctive treatment to standard psychotherapy in a placebo-controlled double-blind study of 70 recently detoxified alcohol subjects (Volpicelli et al. 1988; Volpicelli et al. 1992). The results showed that naltrexone-treated patients reported lower levels of alcohol craving, fewer drinks consumed per occasion, fewer drinking days, and lower rates of relapse than did placebo-treated patients. Differences in relapse rates were most pronounced among subjects who "sampled" alcohol and strongly favored naltrexone.

Volpicelli's initial findings have been replicated and extended by this author's research group (O'Malley et al. 1992). Ninety-seven alcohol-dependent subjects received 50 mg of naltrexone or placebo and either coping skills/relapse prevention therapy or supportive therapy for 12 weeks. Consistent with Volpicelli's findings, naltrexone-treated patients relapsed at a lower rate than patients who received placebo (see figure 1) irrespective of psychotherapy condition. Evidence was also found,

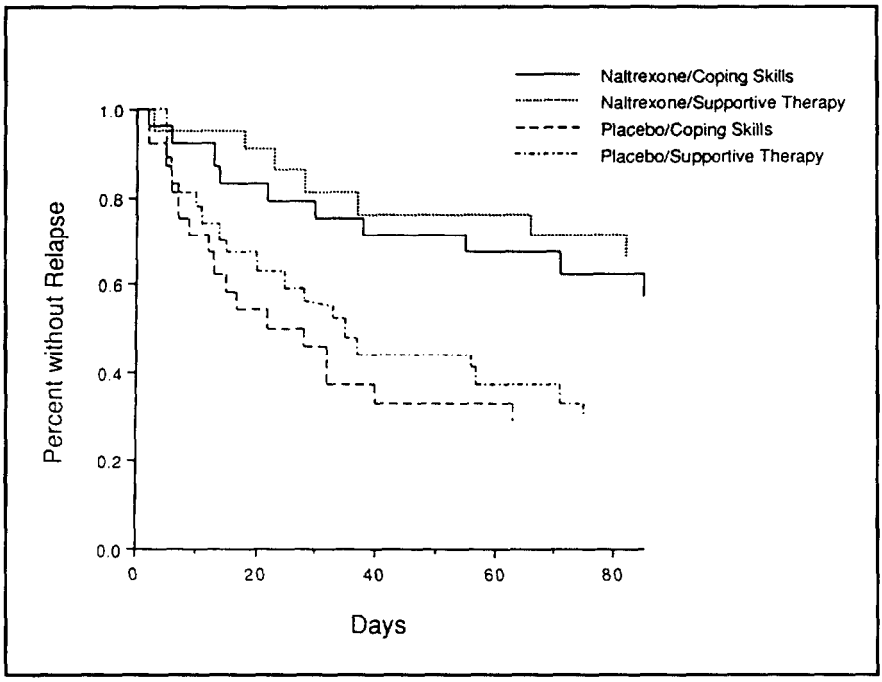

FIGURE 1. *Rates of never relapsing by treatment group reported by O'Malley et al. 1992 (N = 97).*

however, that naltrexone improved abstinence rates when combined with a supportive therapy in which the goal of abstinence was unambiguous. Taken together, these two studies suggest that naltrexone can support a patient's commitment to abstinence and reduce the likelihood that loss-of-control drinking occurs if drinking is initiated. As such, naltrexone appears to address defining features of alcohol dependence including the primacy of alcohol consummatory behavior and impaired control over drinking behavior (Meyer 1989; Meyer and Kranzler 1988).

Furthermore, many of the gains associated with naltrexone therapy appear to be maintained for up to 6 months following cessation of treatment (O'Malley et al. 1993). Preliminary analyses indicate that approximately two-thirds of patients treated with placebo met *Diagnostic and Statistical Manual (DSM)-III-R* criteria for alcohol abuse or dependence at followup, whereas only one-third of naltrexone-treated patients received an alcohol diagnosis. Additional analyses are underway to examine measures of psychosocial functioning and rates of abstinence and relapse over this followup period.

The consistent results across these two independent investigations suggest that naltrexone is an effective pharmacological adjunct to psychosocial treatments for alcohol dependence. Based on these studies, a number of recommendations for using naltrexone in the treatment of alcohol dependence can be made, although innumerable questions remain about strategies to maximize the effective use of naltrexone. The goal of this chapter will be to discuss issues that should be considered in the use of naltrexone as a treatment for alcohol dependence, specifically focusing on the integration of psychosocial interventions.

Dose and Duration of Treatment

In clinical practice, pharmacotherapists often are concerned about providing the patient with an adequate medication dose. There is little research, however, on the dose-response relationship for naltrexone treatment of alcoholism. Consistent with the dose used for narcotic addiction, 50 mg daily was shown to be efficacious in the two placebo-controlled trials of alcoholism (O'Malley et al. 1992; Volpicelli et al. 1992). In a study of heavy drinkers, Bohn (1993) found that subjects significantly reduced their drinking with brief counseling and either 25 mg or 50 mg naltrexone daily, suggesting that low-dose naltrexone may be effective in this population. Whether higher doses lead to greater reductions in drinking behavior remains to be determined.

The potential benefits from higher doses must be weighed against the risk of increased side effects. Higher doses of naltrexone (e.g., 1,400 to 2,100 mg per week) have been shown to be associated with greater risk of hepatocellular toxicity. The occurrence of significant side effects can also reduce medication compliance. Between 5 and 10 percent of alcohol-dependent patients treated with naltrexone discontinued the medication because of side effects, primarily nausea and vomiting (O'Malley et al. 1992; Volpicelli et al. 1992). Consequently, a number of investigators now are prescribing 25 mg of naltrexone for the initial dose and then increasing the dose to 50 mg in an effort to reduce initial drop-out due to side effects.

In addition to questions of dosage, the optimal duration of treatment with naltrexone remains to be determined. The two extant clinical trials were 12 weeks (O'Malley et al. 1992; Volpicelli et al. 1992). Given that alcohol dependence is a syndrome characterized by relapse, it will be important to determine whether a long-term maintenance approach enhances treatment outcome. Extended treatment, for example, may be

particularly crucial for individuals who have more severe alcohol problems. As an alternative, short-term initial treatment with naltrexone combined with the possibility of resuming naltrexone during high-risk periods (e.g., the holidays) may be an effective maintenance strategy. Annis and Peachy (Annis 1991; Peachey and Annis 1985, pp. 199-216) have proposed and studied a similar two-phase treatment approach integrating the use of calcium carbamide, an alcohol sensitizing agent, and relapse prevention techniques. In this approach, continuous calcium carbamide coverage is provided to initiate a stable period of abstinence. As a maintenance strategy, calcium carbamide is utilized primarily in high-risk situations that are identified by the patient, and this use is gradually discontinued as the patient develops alternative coping strategies for dealing with high-risk situations (Annis 1991).

MEDICATION COMPLIANCE

An important factor affecting dose response is medication compliance. Although compliance with naltrexone by alcohol-dependent patients appears to be substantially better than compliance reported in studies of opiate addicts taking naltrexone or studies of alcoholics taking disulfiram (Callahan et al. 1976; Fuller et al. 1986), subjects in early medication trials are likely to be more compliant than patients treated outside of research protocols (Bulpitt 1983). As a result, consideration should be given to strategies intended to increase compliance and consequently maximize treatment outcome. In this regard, much can be learned from the disulfiram literature and the literature on the use of naltrexone in opiate addiction. Better abstinence rates have been found when spouses or treatment staff supervise disulfiram administration compared to when the patient self-administers medication (Azrin et al. 1982; O'Farrell and Bayog 1986). Among opiate addicts, family involvement with patients receiving naltrexone therapy was shown to improve treatment retention and outcome (Anton et al. 1981). Monitoring of medication compliance by opiate addicts has been made more practical by having treatment staff administer naltrexone 3 times per week with 100 mg given on Monday and Wednesday and 150 mg given on Friday, rather than having the patient take 50 mg daily.

Other strategies developed primarily to monitor compliance in medication trials, such as riboflavin markers and microprocessor-based monitoring systems, could be incorporated into behavioral strategies to enhance compliance (Kruse and Weber 1990). Microprocessor-based monitoring

systems use microelectronics embedded in pill-bottle caps to record the date and time that a patient opens his or her pill bottle. As a tool to improve compliance, the data obtained with the cap could be used to give the patient feedback about medication compliance, to help the patient solve problems about situations in which he or she fails to take the medication, and to illustrate to the patient the relationship between compliance and treatment outcome.

INTENSITY OF PSYCHOSOCIAL TREATMENT

Paralleling the issue of medication dose, the "dose" of the psychosocial treatment provided with naltrexone also can be varied in order to achieve optimal treatment response. In treating a population of severely alcohol-dependent subjects who initially required medical detoxification, Volpicelli and colleagues (1992) used naltrexone in the context of an intensive month-long day treatment program followed by twice-weekly therapy. With a less dependent population, O'Malley and colleagues (1992) provided naltrexone as an adjunct to less intensive once-weekly outpatient individual psychotherapy. Although the majority of patients treated with naltrexone in this author's study did well, the group that relapsed tended to be distinguished by having previous treatment failures. One might speculate that this subset of patients would have benefited from an increase in the frequency of sessions or transfer to a partial hospital program while continuing on naltrexone.

Consequently, research is needed on the psychosocial interventions to combine with naltrexone, specifically addressing the patient population to be treated. While it seems likely that weekly contact with a treating professional is important in the initiation of abstinence with naltrexone, the frequency and type of psychosocial intervention needed beyond that remains to be determined. As the data accrue on naltrexone's efficacy, for example, primary care physicians may prescribe naltrexone to alcohol-dependent patients under their care, provide simple advice, and conduct periodic monitoring of their liver functioning and clinical response to the medication. Several studies (Chick et al. 1985; Kristenson et al. 1982; Wallace et al. 1988) have shown that simple advice offered by primary care providers has a beneficial effect on drinking behavior compared to no intervention. The data do not exist about whether or not primary care interventions provided together with naltrexone treatment are effective and, if they are, for whom they work. Given that 60 percent of alcohol abusers make at least one ambulatory

health care visit during a 6-month period and are unlikely to attend specialized alcohol treatment clinics (Shapiro et al. 1984), the potential significance of this minimal intervention cannot be underestimated.

At the same time, an argument can be made that a more intensive intervention may be beneficial for individuals with significant alcohol problems. Although some studies have failed to find an advantage on drinking-related outcomes for extended clinic treatment over a single session of advice (Chick et al. 1988; Edwards et al. 1976) these treatments were not provided in conjunction with an effective pharmacotherapy. Data from this author's research, for example, indicate that among patients pharmacologically supported by naltrexone, those who were provided with concurrent coping skills training were less likely to relapse if drinking was initiated than those who were given supportive psychotherapy. The syndrome of alcohol dependence, while perhaps best characterized by loss-of-control drinking, is often accompanied by a wide range of psychosocial difficulties, including restricted leisure time activities, impaired interpersonal functioning, and legal and vocational difficulties. These problems are targeted by coping skills therapy, which may lead to better long-term adjustment. Consistent with this hypothesis, it was found that patients on naltrexone who received coping skills therapy tended to have better adjustment in psychological functioning and depressed mood than patients who received naltrexone and supportive therapy.

As yet unexplored is the value of beginning naltrexone treatment in an inpatient setting. While the opportunity to drink is minimized on an inpatient unit, several advantages may derive from beginning naltrexone at that time. Numerous studies have demonstrated that discharge from an inpatient treatment program is an extremely high-risk period for resumption of drinking, and that many patients fail to attend aftercare sessions following discharge (Costello 1975). If patients were started on naltrexone prior to leaving the hospital, the risk of a full-blown relapse could be reduced should the patient sample alcohol following discharge. Furthermore, participation in aftercare may be enhanced if the patient is motivated to continue on naltrexone.

Inpatient naltrexone treatment also may provide an opportunity to "inoculate" the patient against alcohol-related cues that elicit conditioned craving (Siegel 1983, pp. 207-246; Wikler, 1965, pp. 85-100). In addition to the finding that naltrexone prevented relapses following an alcoholic drink, data from Volpicelli's study and this author's research

indicate that naltrexone may have an effect on craving that does not depend on sampling of alcohol. It was found, for example, that patients treated with naltrexone and supportive psychotherapy were less likely to initiate drinking than patients treated with placebo. Anecdotally, patients with high baseline levels of craving for alcohol report that they still thought about alcohol once they began naltrexone, but that the urge to act on the thought was diminished, and that, over time, the frequency of thoughts about drinking also diminished.

Stewart, de Wit, and Eikelboom (1984) have argued that conditioned stimuli associated with drug use can elicit neural states that are similar to those produced by the drug itself and thereby increase the probability of drug-related thoughts and behaviors. Extrapolating from this theory, cues associated with drinking may act like a priming dose of alcohol and elicit an appetitive motivational response, perhaps through conditioned endogenous opioid release. If naltrexone blocks this response to drinking-related stimuli, these alcohol-related cues may lose their ability to elicit craving, alcohol-related thoughts, and alcohol-seeking behavior with repeated exposures.

Based on this hypothesis, cue exposure techniques could be combined with naltrexone in order to systematically extinguish the appetitive value of these cues. Cue exposure techniques typically involve presenting an alcoholic with repeated prolonged exposure to cues that elicit a desire to drink, but with instructions not to drink (Cooney et al. 1987; Monti et al. 1987). A variety of alcohol-related cues are used including the sight and smell of alcoholic beverages and induction through imagery of affective states associated with drinking. The strongest alcohol-related cue is actual alcohol consumption, which Sinclair (1990) argues is necessary for an extinction program using opiate antagonists. Because exposure to alcohol-related cues may trigger a relapse in an outpatient, cue exposure is best implemented in an inpatient setting where the opportunity to drink can be limited. Whether cue exposure techniques will enhance the efficacy of naltrexone treatment remains to be determined by research on the effect of naltrexone on reactivity to alcohol-related cues and research examining whether or not naltrexone-induced changes in cue reactivity translate to improvements in treatment outcome.

Ultimately, greater knowledge of the mechanisms underlying the effect of naltrexone on alcohol consumption will help researchers to develop more specific treatments. If naltrexone reduces the urge to drink and enhances abstinence rates, then strategies to enhance the patient's commitment to

abstinence could be developed. If the primary effect of naltrexone is on loss-of-control drinking once alcohol is sampled, then greater focus should be given to strategies to help the patient prevent a relapse.

PATIENT TREATMENT MATCHING

Efforts to maximize outcome will be informed by exploratory analyses of patient-treatment-matching effects and future studies testing a priori matching hypotheses. Preliminary analyses of this author's data suggest, for example, that baseline levels of alcohol craving interact with medication condition (Jaffe et al. 1993). There was a strong positive relationship between craving at baseline and drinking during treatment for patients on placebo. In contrast, baseline craving did not predict alcohol consumption during treatment for patients receiving naltrexone. Instead, high cravers had outcomes comparable to patients with lower levels of baseline craving, which suggests that naltrexone may be particularly helpful to patients struggling with the urge to drink.

It also is conceivable that previously established patient predictors of response to different forms of psychotherapy may be modified by naltrexone treatment. For example, patients with poor cognitive abilities have tended to fare less well in cognitive behavioral treatments compared to supportive treatments presumably because the task demands of coping skills therapy may be too difficult for these individuals (Kadden et al. 1989). If the patient's cognitive abilities are impaired as a result of heavy drinking, improvements in drinking behavior resulting from naltrexone treatment are likely to result in parallel improvements in the patient's cognitive status. As a result of these improvements, the patient may now be more available for learning and utilizing the techniques taught in cognitive behavioral treatments.

Other potential patient characteristics that may interact with treatments include demographic characteristics (Azrin et al. 1982; Fuller and Roth 1979), severity of alcohol dependence (Babor, unpublished data), and presence and type of co-morbid psychopathology (Kadden et al. 1989; McLellan et al. 1983). Finally, patient characteristics may influence the ultimate goal of treatment. Bohn's research (1993) suggests that naltrexone may have benefit in reducing the level of alcohol consumption for individuals who are drinking heavily but who do not meet criteria for alcohol abuse or dependence. For this subset, education about

nonhazardous drinking levels and the development of drinking moderation skills may be appropriate goals of treatment.

REFERENCES

Annis, H.M. A cognitive-social learning approach to relapse: Pharmacotherapy and relapse prevention counseling. *Alcohol Alcohol* Suppl 1:527-530, 1991.

Anton, R.F.; Hogan, I.; Jalali, B.; Riordan, C.E.; and Kleber, H.D. Multiple family therapy and naltrexone in the treatment of opiate dependence. *Drug Alcohol Depend* 8:157-168, 1981.

Azrin, N.H.; Sisson, R.W.; Meyers, R.; and Godley, M. Alcoholism treatment by disulfiram and community reinforcement therapy. *J Behav Ther Exp Psychiatry* 13:105-112, 1982.

Babor, T.F. "Experimental Design, in Project on Identification and Management of Alcohol Related Problems." Unpublished manuscript.

Bohn, M. "Randomized Trial of Safety and Efficacy of 25 versus 50 mg Naltrexone and Brief Counseling to Reduce Heavy Drinking." Paper presented at the annual meeting of the Research Society on Alcoholism, San Antonio, TX, June 22, 1993.

Bulpitt, C.J. *Developments in Biostatistics and Epidemiology: Randomised Controlled Clinical Trials.* Boston, London: The Hague, 1983.

Callahan E.J. et al. Comparison of two naltrexone treatment programs: Naltrexone alone versus naltrexone plus behavior therapy. In: Julius, D., and Renault, P., eds. *Narcotic Antagonists: Naltrexone.* National Institute on Drug Abuse Research Monograph 9. DHEW Pub No, (ADM)76-387. Washington, DC: Supt. of Docs., U.S. Govt. Print. Off., 1976. pp. 150-157.

Chick, J.; Lloyd, G.; and Crombie, E. Counseling problem drinkers in medical wards: A controlled study. *Br Med J* 290:965-967, 1985.

Chick, J.; Ritson, G.; Connaughton, J.; and Stewart, A. Advice versus extended treatment for alcoholism: A controlled study. *Br J Addict* 83:159-170, 1988.

Cooney, N.L.; Gillespie, R.A.; Baker, L.H.; and Kaplan, R.F. Cognitive changes after alcohol cue exposure. *J Consult Clin Psychol* 55: 150-155, 1987.

Costello, R.M. Alcoholism treatment and evaluation. In search of methods. II. Collation of two-year follow-up studies. *Int J Addict* 10:857-867, 1975.

Edwards, G.; Gross, M.M.; Keller, M.; and Moser, J. Alcohol-related problems in the disability perspective. *J Stud Alcohol* 37:1360-1382, 1976.

Froelich, J.C. and Li, T.K. Opioid peptides. In: Deitrich, R., and Galanter, M., eds. *Recent Developments in Alcoholism: Ten Years of Progress.* Vol. 11. New York: Plenum Press, 1993. pp. 187-205.

Fuller, R.K.; Branchey, L.; Brightwell, D.R.; et al. Disulfiram treatment of alcoholism: A Veterans Administration cooperative study. *JAMA* 256:1449-1455, 1986.

Fuller, R.K., and Roth, H.P. Disulfiram for the treatment of alcoholism: An evaluation in 128 men. *Ann Intern Med* 90:901-904, 1979.

Jaffe, A.; O'Malley, S.; Chang, G.; Schottenfeld, R.S.; Meyer, R.; Rode, S.; and Rounsaville, B. "Matching Patients to Naltrexone, Supportive Therapy, and Coping Skills Therapy: A Posttreatment Analysis." Paper presented at the annual meeting of the Research Society on Alcoholism, San Diego, CA, June 15, 1993.

Kadden, R.M.; Cooney, N.L.; Getter, H.; and Litt, M.D. Matching alcoholics to coping skills or interactional therapies: Posttreatment results. *J Consult Clin Psychol* 57:698-704, 1989.

Kosten, T.R., and Kleber, H.D. Strategies to improve compliance with narcotic antagonists. *Am J Drug Alcohol Abuse* 10(2):249-266, 1984.

Kristenson, H.; Trell, E.; and Hood, B. Serum of glutamyl-transferase in screening and continuous control of heavy drinking in middle-aged men. *Am J Epidemiol* 114:862-872, 1982.

Kruse, W., and Weber, E. Dynamics of drug regimen compliance - its assessment by microprocessor-based monitoring. *Eur J Clin Pharmacol* 38:561-565, 1990.

Litten, R.Z., and Allen, J.P. Pharmacotherapies for alcoholism: Promising agents and clinical issues. *Alcohol Clin Exp Res* 15(4):620-633, 1991.

McLellan, A.T.; Woody, G.E.; Luborsky, L.; O'Brien, C.P.; and Druley, K.A. Increased effectiveness of substance abuse treatment: A prospective study of patient-treatment "matching." *J New Ment Dis* 171:597-605, 1983.

Meyer, R.E. Prospects for a rational pharmacotherapy of alcoholism. *J Clin Psychiatry* 50:403-412, 1989.

Meyer, R.E., and Kranzler, H.R. Alcoholism: Clinical implications of recent research. *J Clin Psychiatry* (Suppl) 49:8-12, 1988.

Miller, W.R., and Hester, R.K. The effectiveness of alcoholism treatment: What research reveals. In: Miller, W.R., and Heather, N., eds. *Treating Addictive Behaviors: Processes of Change.* New York: Plenum Press, 1986.

Monti, P.M.; Binkoff, J.A.; Zwick, W.R.; Abrams, D.B.; Nirenberg, T.D.; and Liepman, M.R. Reactivity of alcoholics and nonalcoholics to drinking cues. *J Abnorm Psychol* 96:122-126, 1987.

O'Farrell, T.J., and Bayog, R.D. Antabuse contracts for married alcoholics and their spouses: A method to maintain Antabuse ingestion and decrease conflict about drinking. *J Subst Abuse Treat* 3:1-8, 1986.

O'Malley, S.S.; Jaffe, A.; Chang, G.; Schottenfeld, R.S.; Meyer, R.; and Rounsaville, B. Naltrexone and coping skills therapy for alcohol dependence: A controlled study. *Arch Gen Psychiatry* 49:881-887, 1992.

O'Malley, S.S.; Jaffe, A.; Chang, G.; Rode, S.: and Rounsaville. R. "Naltrexone and Coping Skills Therapy for Alcohol Dependence: 6 Month Follow-up Findings." Paper presented at the annual meeting of the Research Society for Alcoholism, San Antonio, TX, June 22, 1993.

Peachy, J.E., and Annis, H.M. New strategies for using the alcohol-sensitizing drugs. In: Naranjo, C.A., and Sellers, E.M., eds. *Research Advances in New Psychopharmacological Treatments for Alcoholism.* Amsterdam: Elsevier, 1985.

Shapiro, S.; Skinner, E.A.; and Kessler, L.G. Utilization of health and mental health services: Three epidemiologic catchment area sites. *Arch Gen Psychiatry* 41:971-978, 1984.

Siegel, S. Classical conditioning, drug tolerance, and drug dependence. In: Smart, R.; Glaser, F.; Israel, Y.; Kalant, H.; Popliam, R.; and Schmidt, W., eds. *Research Advances in Alcohol and Drug Problems.* Vol. 7. New York: Plenum Press, 1983.

Sinclair, J.D. Drugs to decrease alcohol drinking. *Ann Med* 22:357-362, 1990.

Stewart, J.; de Wit, H.; and Eikelboom, R. Role of unconditioned and conditioned drug effects in the self-administration of opiates and stimulants. *Psychol Rev* 91(2):251-268, 1984.

Volpicelli, J.R.; O'Brien, C.P.; Alterman, A.I.; and Hayashida, M. "Naltrexone and the Treatment of Alcohol-dependence: Initial Observations." Paper presented at the satellite symposium of the 1988 meeting of the Society for Neuroscience, Toronto, Ontario, November 12, 1988.

Volpicelli, J.R.; Alterman, A.I.; Hayashida, M. Naltrexone in the treatment of alcohol dependence. *Arch Gen Psychiatry* 49:876-880, 1992.

Wallace, P.; Cutler, S.; and Haines, A. Randomized controlled trial of general practitioner intervention in patients with excessive alcohol consumption. *Br Med J* 297:663-668, 1988.

Wikler, A. Conditioning factors in opiate addiction and relapse. In: Wilner, D., and Kassenbaum, G., eds. *Narcotics.* New York: McGraw-Hill, 1965.

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Disulfiram (Antabuse) Contracts in Treatment of Alcoholism

Timothy J. O'Farrell, John P. Allen, and Raye Z. Litten

INTRODUCTION

Alcoholism is a major public health problem in the United States (National Institute on Alcohol Abuse and Alcoholism 1990) and throughout much of the world (World Health Organization 1977). It is the most prevalent psychiatric disorder in the United States (Helzer et al. 1991, pp. 81-115). Development of effective treatments for alcoholism, including the use of medications that reduce drinking, has been an important public health goal for many years (National Academy of Sciences 1990). Disulfiram (Antabuse) is a medication that inhibits metabolism of acetaldehyde, a toxic breakdown product of alcohol, and produces unpleasant symptoms (flushing, headache, nausea, vomiting, dizziness, light-headedness, tachycardia) if a person consumes alcohol. The patient who stops taking disulfiram can experience the disulfiram-alcohol reaction for up to 14 days (and generally for at least 4 to 5 days) after discontinuing ingestion of disulfiram. The rationale for disulfiram in treating alcoholism is that most alcoholics taking disulfiram will not drink for fear of getting sick. Disulfiram thus prevents impulsive drinking in response to acute craving or stressors. Of course disulfiram as a deterrent to drinking among alcoholics, like all medications, is only effective for as long as the patient complies with taking the disulfiram. Therefore, this chapter will review briefly the use of disulfiram in treating alcoholism with a special emphasis on the use of behavioral contracts between the alcoholic and a concerned significant other to maintain compliance with disulfiram.

Classic Study of Disulfiram by Fuller and Colleagues 1986

In their classic large-scale clinical trial, Fuller and colleagues (1986) randomly assigned male alcoholics to one of three treatment conditions: (1) 250 mg of disulfiram (N = 202); (2) 1 mg of disulfiram (N = 204), a control for the threat of the disulfiram-alcohol reaction; or (3) no disulfiram (N = 199), a control for the counseling that all participants received. All alcoholics in this study were scheduled to receive weekly outpatient counseling for 6 months followed by biweekly counseling

sessions for the final 6 months. Followup interviews were scheduled to occur bimonthly during the study year. Study participants on average were middle aged (42 years mean age), ethnically diverse (54 percent white), moderately socially stable (54 percent married, 70 percent employed) chronic alcoholics (12 years of alcohol abuse).

The Fuller and colleagues (1986) study produced four major results. First, a customary therapeutic dose (250 mg) of disulfiram was not superior to placebo (1 mg) or no disulfiram in producing abstinence, reducing time to first drink, or improving social or employment status among male alcoholic patients. Second, failure of patients to take the drug as prescribed may have rendered disulfiram ineffective. In fact, only 20 percent of the subjects were judged "good compliers" as evidenced by consistent urinalysis results positive for riboflavin, the biochemical marker of disulfiram employed. Third, better compliance was related to more abstinence. A higher percentage of compliant than noncompliant patients was continuously abstinent for the 1 -year followup period (43 percent for the compliant versus 8 percent for the noncompliant, $p < .001$). Fourth, patient acceptance of disulfiram was low. Only 38 percent of the 1,618 alcoholics who met study criteria and were medically cleared to take disulfiram agreed to enter the study and possibly take disulfiram. Most study refusals were due to patients' reluctance to take disulfiram.

The Fuller and colleagues (1986) study showed that disulfiram was not effective because of serious problems with patient acceptance and compliance. However, abstinence was observed among patients who took the medication consistently. Further, the low patient acceptance may have been related to the fact that the disulfiram was not an integral part of the alcoholism counseling used. Findings such as these underscore the importance of techniques to increase compliance with disulfiram. After an overview of such techniques, the use of behavioral contracts to increase compliance and to make disulfiram an integral part of psychosocial treatments for alcoholism will be considered in detail.

Overview of Techniques to Increase Compliance With Disulfiram

Varied strategies to enhance disulfiram compliance have been devised. This overview will examine implants, patient instructional sets, and incentives, each of which are covered in depth elsewhere (Allen and Litten 1992).

Disulfiram Implants. The most potent guarantee for disulfiram compliance would seem to be physical implant to release disulfiram into the bloodstream at a consistent rate and at a level sufficient to cause an adverse physical reaction should the patient drink. Disulfiram implants have been available for 30 years, and more recent investigations on implants have been reasonably well controlled (e.g., Johnsen et al. 1990; Wilson et al. 1984). Such studies have identified serious limitations, however, to disulfiram implants. First, most such depots fail to release adequate levels of disulfiram. Second, the bolus of the implant under the skin has led to adverse effects of infections and rejection after the implant surgical procedure. Third, controlled studies have not found superior outcomes for alcoholics treated with currently available implants. These results led Allen and Litten (1992) to conclude that disulfiram implants, for biochemical reasons per se, have been largely ineffective.

Patient Instructions. An alternative strategy to enhance attractiveness of taking disulfiram is modification of patient instructions and expectations for the medication. Two different approaches have shown promising results in initial investigations. Duckert and Johnsen (1987) allowed patients a choice of methods for using disulfiram ranging from the conventional long-term use to prevent drinking to infrequent, periodic use for specific reasons chosen by the patient (e.g., to prevent drinking in a high-risk situation). Kofoed (1987) significantly increased disulfiram compliance among alcoholic outpatients by informing them and their case managers of results of carbon disulfide breathalyzer tests taken at each counseling session to corroborate extent of recent disulfiram use.

Tangible Incentives. Other studies have considered the effectiveness of tangible incentives for taking disulfiram. Most of the incentives that have been tried relate in some way to circumstances and conditions specific to the patient group of interest. Among these have been (1) less restrictive probation for individuals charged with alcohol-related offenses (Boume et al. 1966; Brewer and Smith 1983); (2) methadone contingency for methadone patients with alcohol problems (Liebson et al. 1973, 1978); (3) money returned from a security deposit made by alcoholics initiating outpatient counseling (Bigelow et al. 1976); (4) job security for industrial workers referred by their employers for drinking-related job problems (Robichaud et al. 1979); (5) continued affiliation with the treatment program in which the patient is currently enrolled rather than discharge from the program or referral to another clinic (Bickel et al. 1989; Sereny et al. 1986); and (6) more frequent clinic visits as a form of psychological

incentive among socially isolated, inner-city alcoholics (Gerrein et al. 1973).

While each of these studies suffers from specific methodological limitations, the findings uniformly suggest better disulfiram compliance and more favorable clinical outcomes for those who received an incentive for taking disulfiram. In such studies, direct observation of the patient taking disulfiram by a court or clinic staff person, often referred to as "supervised" disulfiram, was typically part of the procedure to assess compliance so that the incentive could be provided. Observed or supervised disulfiram without specified incentives is the basis for disulfiram contracts and other compliance enhancement procedures-the subject of the remainder of this chapter.

DISULFIRAM CONTRACTS AND SUPERVISED DISULFIRAM

Description and History of Disulfiram Contracts

"Behavioral contracting" is generally done with both the client and a significant other, usually the spouse, in the client's living environment. Interestingly, behavioral agreements typically do not explicitly stipulate tangible consequences for taking or refusing disulfiram, although they do specify social reinforcers, e.g., expression of appreciation by the spouse when the alcoholic takes disulfiram. These agreements also require that both the patient and the significant other formally and publicly commit themselves to observation of disulfiram use.

Figure 1 provides a sample disulfiram contract taken from O'Farrell and Bayog (1986), who describe the clinical procedures involved in some detail including methods for dealing with common resistances and problems encountered. Two slightly different versions of the disulfiram contract appeared in the literature at about the same time.

The Behavioral Marital Therapy (BMT) version, first described by Miller and Hersen (1975) and Miller (1976) provides for observed disulfiram with mutual thanking by alcoholic and spouse plus a commitment to refrain from discussions (except during BMT sessions) about the alcoholic's drinking (see item 3 of the contract in figure 1).

DISULFIRAM (ANTABUSE) CONTRACT

In order to help John Doe with his/her own self-control and to bring peace of mind to Mary, his/her wife, John and Mary agree to the following arrangement.

John's Responsibilities	Mary's Responsibilities
1. John takes Antabuse each day.	1. Observes the Antabuse being taken and records that she observed it on the calendar provided.
2. Thanks Mary for observing the Antabuse.	2. Thanks John for taking the Antabuse and shows appreciation when he/she takes it.
3. If necessary, requests that Mary not mention past drinking or any fears about future drinking.	3. Does not mention past drinking or any fears about future drinking.
4. Refills Antabuse prescription before it runs out.	4. Reminds when prescription needs refilling.

EARLY WARNING SYSTEM: If at any time Antabuse is not taken and observed for 2 days in a row, John or Mary should contact Dr. O'Farrell (Phone No: xxx xxxx) immediately.

LENGTH OF CONTRACT: This agreement covers the time from today until 11/30/94. It cannot be changed unless John, Mary and Dr. O'Farrell discuss the changes in a face-to-face meeting of at least 30 minutes.

Date: 5/16/94 John Doe Mary Doe

Timothy J. O'Farrell, Ph.D.

FIGURE 1. *Sample disulfiram contract used in behavioral marital therapy with alcoholics.*

Like all disulfiram contracts, the BMT version seeks to maintain disulfiram ingestion and abstinence. The BMT version also seeks to restructure the couple's relationship to reduce their conflicts about past drinking or the likelihood of future drinking and to decrease the spouse's anxiety, distrust, and need to control the alcoholic. The BMT version tries to deal with these presumed relationship dynamics of the early

sobriety period in order to increase support for abstinence and reduce the risk of relapse (O'Farrell 19933).

The Community Reinforcement Approach (CRA) version derives from Azrin's (I 976) attempt to augment the effectiveness of his CRA approach to alcoholism treatment (Hunt and Azrin 1973) by adding a disulfiram component to it. The CRA version of the disulfiram contract is identical to the BMT version except that CRA does not include item 3 restricting discussions about drinking. Studies of each of these two approaches are considered next.

Behavioral Marital Therapy Studies of Disulfiram

Miller and Hersen (1975) reported a case in which a disulfiram contract and BMT were used to promote abstinence and reduce marital conflict. The 49-year-old factory worker husband, whose 10-year history of alcoholism was characterized by many arrests, car accidents, and marital problems, had been consuming a pint to a fifth of vodka daily prior to his admission to a hospital for alcoholism treatment. The wife had decided to divorce him if he did not stop drinking. Pretreatment assessment revealed very little positive communication and extensive negative comments by the wife about drinking (e.g., blaming for past drinking, threats about future drinking). Treatment consisted of BMT sessions to increase constructive communication and a contract specifying daily disulfiram intake by the husband and cessation of discussion about drinking by the wife. (The contract was quite similar to the model in figure 1.) Treatment started with weekly sessions in the hospital with the husband visiting home each weekend and continued on an outpatient basis biweekly for 3 months and monthly thereafter for 3 months. Nine-month followup revealed that the husband had remained abstinent and was still taking disulfiram daily. In addition, the couple was communicating more constructively and going out together regularly. The wife had stopped mentioning the past and was generally more pleasant. The couple had handled several problems quite well. The positive BMT results from the Miller and Hersen (1975) case report, along with similar affirming results from other early case reports and uncontrolled studies of BMT, led to controlled studies of BMT. The Counseling for Alcoholics' Marriages (CALM) Project studies of BMT included disulfiram contracts as part of the Project CALM BMT program (O'Farrell 1993a, pp. 170-209).

In an initial Project CALM study (known as the CALM-l study), O'Farrell and colleagues (O'Farrell et al. 1985, 1992) investigated the effect of adding BMT couples group treatment with a disulfiram contract to individually oriented outpatient treatment of married male alcohol abusers. Thirty-six couples, in which the husband had recently begun individual alcohol counseling that included a disulfiram prescription, were randomly assigned to (1) 10 weekly sessions of a BMT (behavioral rehearsal of communication skills and marital agreements) couples group plus a disulfiram contract; (2) 10 weeks of an interactional (largely verbal interaction and sharing of feelings) couples group without a disulfiram contract; or (3) a no-marital-treatment control group. Results at the end of treatment (O'Farrell et al. 1985) showed that adding BMT plus a disulfiram contract to individual alcoholism counseling produced significant improvements in marital and drinking adjustment that were superior to outcomes of individual counseling alone and to individual counseling plus interactional couples therapy. Results during the 2 years after treatment (O'Farrell et al. 1992) showed that alcoholics and their wives who received the additional BMT remained significantly improved on marital and drinking adjustment throughout the 2 years. Although BMT continued to appear superior to individual counseling alone on marital adjustment throughout much of the 2-year followup, the strength and the consistency of findings favoring BMT diminished as time after treatment lengthened. In terms of drinking outcomes during the 2 years after treatment, the addition of BMT no longer produced better results than did interactional couples therapy or individual treatment alone.

The specific contribution of the disulfiram contract to the results observed in the CALM-l study cannot be determined. The disulfiram contract was part of the BMT program. The extent of patients' use of disulfiram was not measured. Still, it seems likely that during treatment the disulfiram contract may have contributed importantly to the lower rate of drinking and drinking-related problems observed in the BMT couples as compared with the other couples who did not use the disulfiram contract. Perhaps after treatment ended, use of the disulfiram contract decreased since BMT no longer produced less drinking than the other treatments. The CALM-l study results suggested the need for a study of treatment methods to maintain the use of the disulfiram contract and the gains produced by BMT, especially for drinking and related behaviors.

Results of CALM-l produced CALM-2, a study to evaluate the usefulness of couples relapse prevention (RP) sessions for maintaining changes in marital and drinking adjustment produced by short-term BMT.

Continued use of the disulfiram contract, especially for individuals suffering more severe drinking problems, was one of the goals of the RP sessions. In this study, after participating weekly for 5 months in a BMT couples program, 59 couples with an alcohol-abusing husband were assigned randomly to receive or not receive 15 additional couples RP sessions over the next 12 months. Outcome measures were collected before and after BMT and at quarterly intervals for the 2-1/2 years after BMT.

The CALM-2 investigation produced three major findings (Cutter et al. 1993; O'Farrell et al. 1993). First, results for the entire sample showed the additional RP sessions produced better outcomes during and for the 6 to 12 months after the end of RP. Specifically, alcohol abusers who received RP after BMT had more days abstinent and used the disulfiram contract more than those who received BMT alone. The superior RP drinking outcomes continued through 18 months followup (i.e., 6 months after the end of RP). Couples who received the additional RP also maintained improved marriages longer (through 24 months followup) than did their counterparts who received BMT only (through 12 months followup). Second, for alcoholics with more severe marital and drinking problems, RP produced better marital and drinking outcomes throughout the 30-month followup period. Specifically, alcoholics with more severe alcohol problems at study entry used the disulfiram contract more (see figure 2) and showed a less steep decline in use of the disulfiram contract (see figure 3) throughout the 30 months after BMT if they received the additional RP than if they did not. Further, alcoholics with more severe marital problems at study entry experienced better marital adjustment and more days abstinent and maintained relatively stable levels of abstinence if they received the additional RP, while their counterparts who did not receive RP had poorer marital adjustment and fewer abstinent days and showed a steep decline in abstinent days in the 30 months after BMT. Third, greater use of the disulfiram contract was associated with more days abstinent and more positive marital adjustment test scores after BMT for all subjects irrespective of the amount of aftercare received.

To summarize, two Project CALM BMT studies of disulfiram contracts have been completed. The CALM-l study showed that adding BMT plus a disulfiram contract to individual alcoholism counseling led to better short-term drinking and marital outcomes than a disulfiram prescription alone accompanied by either an alternative form of couples counseling or

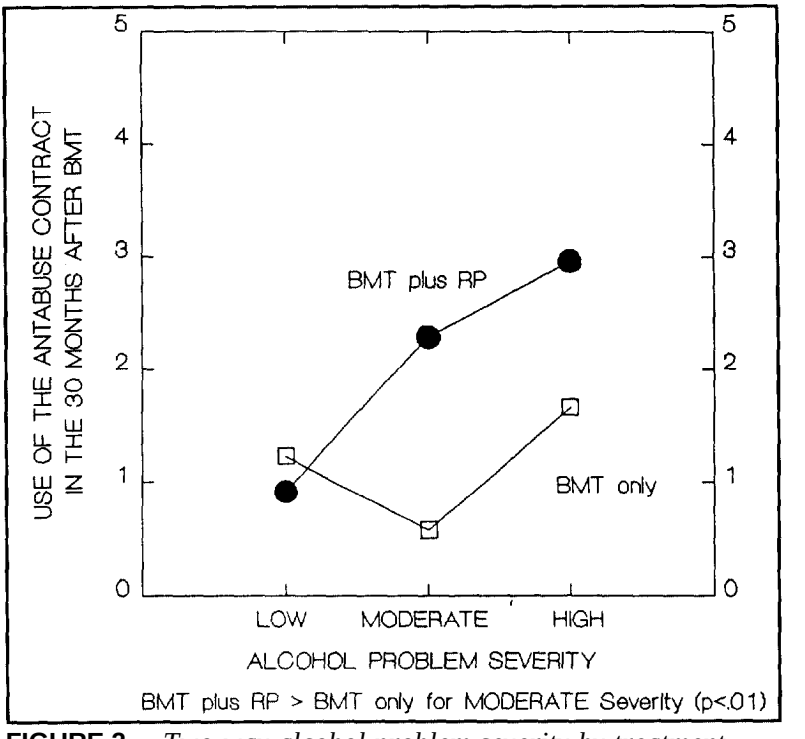

FIGURE 2. *Two-way alcohol problem severity by treatment interaction for use of disulfiram (Antabuse) contract in Cutter and colleagues (1993) CALM-2 study of BMT and disulfiram contract.*

individual counseling alone. Superior BMT drinking results did not persist through the 2-year followup period, possibly because many couples discontinued their disulfiram contract after treatment ended. The CALM-2 study indicated that adding couples RP sessions in the year after BMT enhanced use of the disulfiram contract and yielded better marital and drinking outcomes than BMT alone. These better RP outcomes persisted for 18 to 24 months after BMT for the entire sample and throughout the entire 30 months followup after BMT for those with more severe marital and drinking problems. Thus the Project CALM studies suggest that disulfiram contracts used with BMT are associated with less drinking and greater disulfiram compliance. However, the specific contribution of disulfiram contracts to the multifaceted BMT treatment package remains to be investigated.

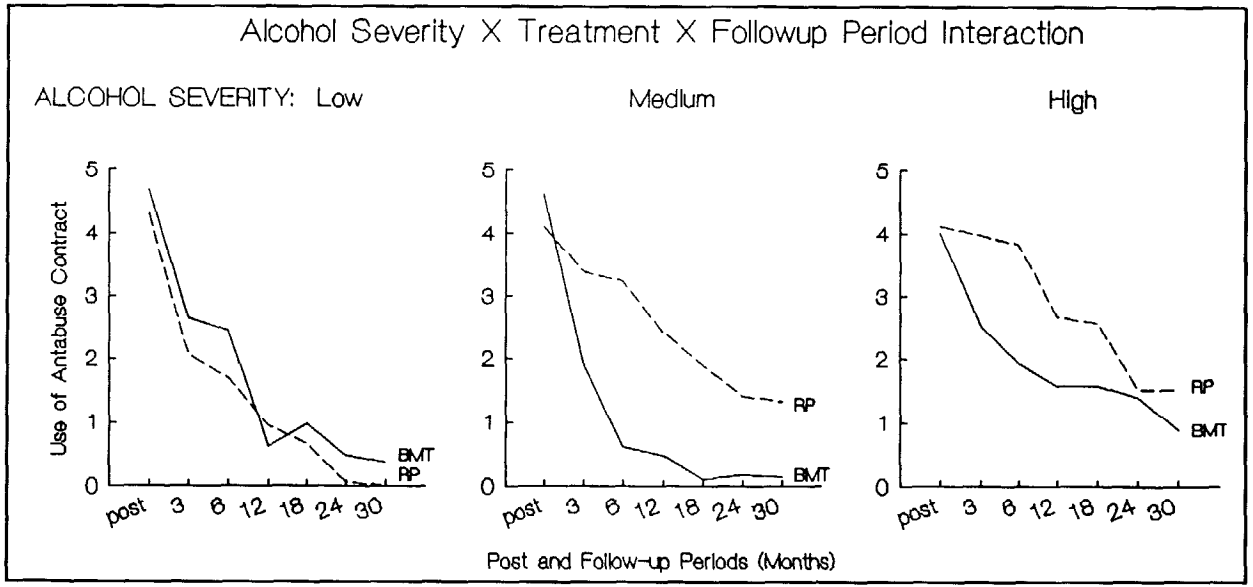

FIGURE 3. *Three-way alcohol problem severity by treatment by time interaction for use of disulfram (Antabuse) contract in Cutter and colleagues (1993) CALM-2 study of BMT and disulfiram contract.*

Community Reinforcement Approach Studies of Disulfiram Contracts

Azrin developed a CRA to treating alcoholics that was based on operant conditioning principles. CRA rearranged community reinforcers such as the job, the family, and the social relations of the alcoholic such that drinking produced a "time-out" from a high density of reinforcement. The results from the initial CRA study convincingly demonstrated that the eight alcoholics who received this CRA counseling drank less, worked more, and spent more time with their families and out of institutions than did a matched control group of eight alcoholics who did not receive these procedures (Hunt and Azrin 1973).

Azrin (1976) attempted to augment the effectiveness of CRA by adding a disulfiram component to it. Subjects were 18 inpatient alcoholic males randomly assigned to CRA with a disulfiram contract or to a matched control group receiving standard alcoholism treatment with general advice to take disulfiram. Several procedures, all of which have become standard in both CRA and BMT studies of the disulfiram contract, were employed with the experimental group to heighten disulfiram compliance. These included (1) instructing the client and significant other on the rationale and benefits of disulfiram as a "chemical time-delay device" to avoid impulsive drinking and its consequences, (2) encouraging the alcoholic to personally request that the other person monitor the use of disulfiram, (3) establishing specific links between taking the medication and recurrent daily activities, (4) monitoring disulfiram administration by the significant other or the counselor, and (5) referring the client to a physician supportive of disulfiram. A formal contract in which the client agreed to take disulfiram (similar to the one in figure 1 except that item 3 was omitted) was signed with the counselor.

In the Azrin (1976) study, 6-month self-report followup measures demonstrated that the CRA with the disulfiram contract was substantially more effective in reducing the number of drinking days than standard treatment with general advice to take disulfiram. Additional followup for 2 years of CRA subjects (followup for the control-group subjects was limited to 6 months) showed continued positive outcomes for CRA subjects on number of days drinking, percent time employed, percent time institutionalized posttreatment, and amount of time spent with the family. The authors also concluded that the CRA with the disulfiram contract was preferable to the previous version of CRA without disulfiram in that the newer strategy reduced drinking and the amount of

CRA counseling time needed. While these results suggest benefits of contracting for disulfiram and of employing a range of enhancement techniques, unfortunately it is not possible to isolate the effects of the disulfiram contract from the remaining elements of CRA itself.

A subsequent CRA study (Azrin et al. 1982) more explicitly evaluated the benefits of disulfiram contracting and compliance aids. Outpatients in a rural community alcoholism clinic who did not suffer co-morbid drug dependence or psychosis were encouraged to take disulfiram and were referred to the agency physician and a nearby pharmacy to obtain the medication. Following the first session, 43 subjects were randomly assigned to one of three treatment conditions:

1. Traditional treatment plus a prescription for disulfiram without special disulfiram contract procedures;

2. Traditional treatment with disulfiram contract procedures similar to those employed in the Azrin (1976) study cited above; or

3. CRA including disulfiram contracting.

Six-month followup in the Azrin and colleagues (1982) study demonstrated that patients in the three conditions differed on number of days on which disulfiram was taken, days drinking, days intoxicated, and average amount of ethanol consumed per drinking episode. There were two major findings: First, patients receiving CRA and a disulfiram contract performed best; those in traditional therapy without disulfiram contract fared worst; those in traditional therapy with a disulfiram contract responded at a level intermediate between the other two groups. Figure 4 suggests that, while the groups differed throughout the followup period, disulfiram use declined appreciably by the second month for the traditional therapy group without the disulfiram contract and decreased quite rapidly thereafter with no disulfiram being taken after 3 months. The clients in the two groups given the disulfiram contract were taking disulfiram about 90 percent of the time initially and showed less of a decrease over time remaining with two-thirds or more days taking disulfiram on average through 6 months followup. Second, the authors found that married or cohabiting clients assigned to the disulfiram contract and traditional treatment performed about as well on the four outcome measures as they did with CRA plus the disulfiram contract.

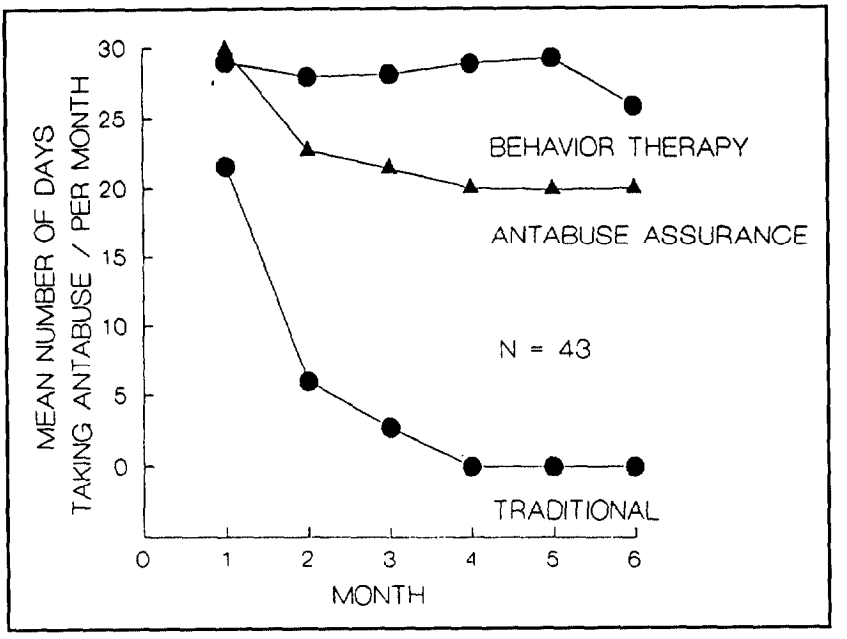

FIGURE 4. *Mean number of days on which disulfiram (Antabuse) was taken during each month (30 days) of the 6 months of followup. Disulfiram was given in the usual manner in the "traditional" group whereas adherence was socially motivated for the "Disulfiram Assurance" group. The "behavior therapy" group received community-oriented reinforcement therapy in addition to the disulfiram assurance program. (Reprinted from Azrin et al. 1982, p. 109, by permission of Pergamon Press.)*

NOTE: Reprinted from *Journal of Behavioral Therapy and Experimental Psychiatry*, Vol. 13, No. 2, Azrin, N.H.; Sisson, R.W.; Meyers, R.; and Godley, M. Alcoholism treatment by disulfiram and community reinforcement therapy, pp. 105-112 (1982), with kind permission from Elsevier Science Ltd., The Boulevard, Langford Lane, Kidlington, 0X5 1GB, UK.

Single clients, however, achieved additional gain from CRA plus disulfiram contract over traditional therapy and disulfiram contract. Table 1 from the Azrin and colleagues (1982) study illustrates this finding.

TABLE 1. *Mean number of days abstinent during the 6th month (30 days) of followup (N = 43).*

	Singles	Couples
Traditional counseling with disulfiram prescription	6.75	17.40
Traditional counseling with disulfiram contract	8.00	30.00
CRA with disulfiram contract	28.30	30.00

Reprinted from Azrin et al. 1982, p. 110. Adapted by permission from Pergamon Press.

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In summary, CRA studies of disulfiram contracts have produced two major findings. First, the disulfiram contract with CRA produces better disulfiram compliance and less drinking than traditional counseling with a disulfiram prescription or simple advice to take disulfiram (Azrin 1976; Azrin et al. 1982). Second, for married or cohabiting clients, a disulfiram contract with either CRA or traditional counseling resulted in better compliance and more abstinence than did traditional counseling with a disulfiram prescription, while single clients required the CRA plus the disulfiram contract to get beneficial outcomes (Azrin et al. 1982). The CRA studies have attracted great interest because they show very good treatment outcomes and clear superiority of CRA over comparison treatments. However, the CRA studies have also been subjected to a number of criticisms. The sample sizes have been small, the followup periods have been limited to 6 months, and some of the followup period has included time in treatment delivery. The intensity, credibility, and content of the traditional counseling control group have been questioned in that the same therapists delivered both CRA and the traditional counseling, raising concerns that therapists may not have been equally

invested in the two treatments. The CRA groups received more sessions than the other groups. The use of films and discussion on the disease of alcoholism for the traditional counseling also has been questioned.

The interest in and criticisms of the disulfiram contract plus CRA studies has led to larger scale, better controlled clinical trials, One of these studies currently is in progress at the University of New Mexico under the direction of William Miller. This study will randomly assign 160 alcoholics at a public alcoholism clinic to one of four treatments:

1. Traditional counseling with encouragement to take disulfiram but without a disulfiram contract;

2. Traditional counseling with a disulfiram contract;

3. CRA with a disulfiram contract;

4. CRA without disulfiram.

Different counselors will deliver CRA and traditional treatments. Counselors will be chosen and trained to be equally committed to each treatment approach. Followup will be conducted periodically for 2 years after the end of each treatment. Results from this study will provide important information about the utility of disulfiram contracts in both CRA and traditional counseling.

Other Studies of Disulfiram Contracts and Supervised Disulfiram

Two other studies of disulfiram contracts or supervised disulfiram have been reported. These studies were not done in the framework of BMT or CRA. The specific disulfiram compliance procedure varied from the versions used in BMT or CRA.

Further research on disulfiram contracting and monitoring with patients and significant others was performed by Keane and colleagues (1984). Male alcoholic inpatients (N = 25) being discharged from a 4-week behaviorally oriented inpatient alcohol treatment program and a significant other (usually the wife) living with them were subjects in the study. All alcoholics agreed to take disulfiram. All significant others also attended a discharge planning session with the alcoholic and counselor, which included videotaped educational material about

disulfiram and the dangers of drinking while taking it. In addition, the significant others were told that they would receive a monthly phone call from a staff member to check on the use of disulfiram and to assist in resolving any apparent difficulties surrounding it. Then subjects were assigned randomly to one of three experimental conditions:

1. No contract/no recording group. While the patient was urged to take the medication daily at 9 p.m., no contract was signed dealing with its use or monitoring.

2. Contract/recording group. The couple agreed that disulfiram would be taken daily in the presence of the monitor followed by signing the date on the contract. Recording sheets were to be mailed back to the clinic on a monthly basis.

3. Contract/recording plus instruction for positive reinforcement. In addition to receiving the same instructions as group 2, participants were encouraged to provide a weekly reinforcement contingent upon taking disulfiram.

Compliance rates in the Keane and colleagues (1984) study appeared quite high. All but one of the subjects in the latter two groups returned their annotated charts to the clinic. Review of pharmacy records demonstrated that a higher percentage of patients in these two groups had their disulfiram prescriptions refilled than did those in group 1, a marginally significant difference ($p < .06$). However, even in group 1, 56 percent of the patients had 3 months of disulfiram prescriptions filled. Monthly interviews with significant others indicated that most patients, regardless of group to which assigned, were continuing to take disulfiram, and that only four subjects were drinking abusively at 3-month followup. There were no significant differences among treatment groups in drinking. Thus the Keane and colleagues (1984) study did not find better clinical results for those who employed the disulfiram contract as compared to those who did not. The short duration of followup and the small sample size may have precluded emergence of convincing evidence of an advantage for the disulfiram contract. The motivational and instructional aspects common to all subjects including the comparison group also must be considered. All subjects started disulfiram after at least 4 weeks of inpatient treatment, and the significant others viewed a videotape on use of disulfiram and its effects with instructions that they would be contacted regularly about the patient's compliance with disulfiram. The motivational and instructional sets

appear to have increased compliance in the noncontract group beyond levels reported by others (Azrin et al. 1982; Fuller et al. 1986).

The final study by Chick and colleagues (1992) represents the largest study of supervised disulfiram to date. Subjects were patients (N = 126) attending seven alcoholism treatment centers in the UK. All subjects had relapsed after previous therapy or other support. Pregnant women were excluded, as were subjects with cardiac disease, co-morbid drug dependence or psychosis, and those showing abnormally high levels of serum bilirubin, aspartate aminotransferase (AST), or alanine aminotransferase (ALT). Patients were already receiving or were offered a range of outpatient counseling and support, which varied among treatment centers. In addition to outpatient counseling, patients were randomly assigned to one of the following:

1. Supervised 200 mg daily dose of disulfiram in which an informant (usually the spouse) supervised daily ingestion of disulfiram by the patient. The informant was encouraged to phone the clinic if the patient refused the medication so that advice could be offered. No written contract, however, was involved, and no formal sanctions were invoked if the patient ceased taking the medication. The more extensive compliance procedures used in BMT and CRA studies of disulfiram contracts were not employed.

2. Supervised use of vitamin C to control for the effects of receiving supervised medication and outpatient counseling. Patients were told this rationale. If they asked further they were told that vitamin C was chosen for the control medication because alcoholics may have vitamin deficiencies, of which this is one.

An independent assessor, blind to the medication received, saw each patient and informant at intake, again at weeks 2 and 4, and monthly thereafter until the final interview at 6 months. Interview questions concerned alcohol consumption, alcohol dependence, and alcohol-related health and social problems. Blood tests to measure alcohol-related liver dysfunction were taken at intake, and after 1, 3, and 6 months of treatment. All data were used on an "intention-to-treat" basis irrespective of patient compliance, and attempts were made to follow up all patients. Fifty-seven patients (i.e., 45 percent of the sample, consisting of 28 on disulfiram, 29 on vitamin C) did not adhere to their assigned treatment, 45 through failure to keep appointments or by withdrawing consent. Followup interviews were not obtained in 20 percent (15 disulfiram

patients, 14 vitamin C patients). Both initial and final blood samples were available in only 57 percent, because at followup some patients were interviewed by telephone; also, at intake and followup some samples were not analyzable because of delay or damage.

Results showed that alcoholics assigned to supervised disulfiram, when contrasted with their counterparts receiving supervised vitamin C, realized significantly greater improvement in the 6 months after as compared with the 6 months before study entry on number of days abstinent, typical weekly alcohol consumption, total alcohol consumption for the 6-month period, and in serum gamma-GT levels-a biochemical marker of recent heavy drinking and its negative acute effects on the liver. Alcohol-related problems (e.g., violent episodes, time off work, police involvement) showed a strong trend ($p < .06$) toward significantly greater improvements in the supervised disulfiram group. At the end of the study, two-thirds of the patients on disulfiram wanted to continue treatment compared with only one-quarter of those on vitamin C ($p < .001$). Furthermore, there were no medically serious adverse reactions from disulfiram-alcohol reactions or from hepatic toxicity. A few patients taking disulfiram developed skin rash, headaches, or tiredness, but there was no disturbance of liver function.

Thus, Chick and colleagues (1992) found that supervised disulfiram plus outpatient counseling produced better outcomes of more abstinence and less drinking and fewer alcohol-related social and health problems than counseling without supervised disulfiram. Importantly too, patients receiving disulfiram did not experience liver problems in this sample screened to be free of liver problems at study entry. In fact, those on disulfiram actually showed decreases in serum GT levels while the control group showed increases. The Chick and colleagues (1992) results particularly merit credibility given the careful outcome evaluation methods used, including blind assessors and inclusion of dropouts in the analyses of the study sample. Certain considerations should, however, be noted in considering these results. There was no control group that received disulfiram without compliance enhancement. Disulfiram compliance was not measured directly. Forty-five percent of patients failed to continue with the assigned treatment, a higher dropout rate than observed in BMT and CRA studies of disulfiram contracts. The BMT and CRA studies used a more complex disulfiram contract that was an integral part of the patients' counseling. Finally, the role of the counseling was difficult to determine since it varied considerably among the treatment centers participating in the study.

SUMMARY AND CONCLUSIONS

Although studies repeatedly demonstrate that alcoholics who consistently take disulfiram experience more favorable drinking outcomes, serious problems with compliance among the majority of alcoholic patients have reduced the effectiveness of disulfiram as a therapeutic adjunct. In general, alcoholism counseling with disulfiram simply prescribed seems no more effective than counseling without disulfiram (Fuller et al. 1986). Problems with compliance as well as problems with acceptance by patients and likely by clinical staff reduce the utility of disulfiram in the treatment of alcoholism.

Implants, incentives, and various forms of observed or supervised disulfiram have been studied as possible solutions to the problems with compliance. Disulfiram implants appear largely ineffective due to failure to release adequate levels of disulfiram and risks of surgical complications and rejection. Newer techniques (see Allen and Litten 1992) may ultimately lead to a more effective implant.

Incentives with personally relevant and obvious reinforcement value such as money, avoidance of incarceration, remaining employed, and continuation of methadone for opiate addicts, have been used effectively. Enhancement strategies with less tangible incentives also show promise. Among these are feedback on results of biochemical measures of disulfiram compliance and continuation in a familiar treatment program. Although each of the studies of incentives suffers from specific methodological limitations, the findings uniformly demonstrate better disulfiram compliance, less drinking, and better clinical outcomes for those who received a meaningful incentive for taking disulfiram.

External monitoring of the patient taking disulfiram to assure compliance is typically used in studies evaluating incentives for taking the medication. Observed or supervised disulfiram in its own right and without tangible incentives also has received increasing attention as a method for enhancing compliance. Incorporation of such a strategy would seem to have potential for wide applicability in alcoholism treatment programs. Three forms of supervised disulfiram have been studied: (1) a written disulfiram contract, such as in BMT, with instructions about the benefits of the disulfiram contract and methods to establish disulfiram use as a daily habit and specifying that the alcoholic will take disulfiram daily while the spouse observes, that the couple will mutually thank each other, and that they will refrain from arguments or

discussions about the alcoholic's drinking; (2) the disulfiram contract used in CRA, which is identical in form to the BMT contract except that talk about drinking is not prohibited; and (3) supervised disulfiram without a written contract, special instructions, or explicit verbal thanking. Studies of these three forms of observed disulfiram have been among the better controlled studies. Each approach has produced very promising results.

A disulfiram contract with BMT produced less short-term drinking than disulfiram accompanied either by couples or individual counseling. Unfortunately, the superior BMT drinking results eroded because many couples discontinued their disulfiram contract after treatment ended (O'Farrell et al. 1985, 1992). Adding couples RP sessions after BMT led to better fulfillment of the disulfiram contract and better drinking and marital outcomes than BMT alone. These better RP outcomes persisted for 18 to 24 months after BMT for the entire sample and throughout the entire 30-month followup after BMT for those with more severe drinking and marital problems (O'Farrell et al. 1993). Thus, disulfiram contracts used with BMT are associated with less drinking and greater disulfiram compliance, while the specific contribution of disulfiram contracts to BMT remains to be investigated.

A disulfiram contract with CRA produced better disulfiram compliance and less drinking than traditional counseling with a disulfiram prescription or advice to take disulfiram (Azrin 1976; Azrin et al. 1982). For married or cohabiting clients, the disulfiram contract with either CRA or traditional counseling produced better compliance and more abstinence than did traditional counseling with a disulfiram prescription, while single clients required the CRA plus disulfiram contract to enjoy favorable outcomes (Azrin et al. 1982).

Supervised disulfiram (without special instructions or written contract) plus outpatient counseling produced better outcomes of more abstinence, less drinking, and fewer alcohol-related social and health problems than counseling without supervised disulfiram (Chick et al. 1992). This was the largest study to date of observed disulfiram or any other strategy to enhance disulfiram compliance. The 4.5 percent dropout rate, however, greatly exceeded that reported by studies of BMT and CRA disulfiram contracts.

To summarize prior research, problems with patient compliance and acceptance have seriously limited the utility of disulfiram as a therapeutic

adjunct in treating alcoholism. Implantation to increase compliance has not been successful to date. Incentives tailored specifically to the patient's current situation (e.g., avoiding jail for alcohol-related offenses), however, have shown significant promise. Observed or supervised disulfiram with its potential for wide applicability also has demonstrated very favorable outcomes in combination with BMT, CRA, and traditional counseling. Results have included increased compliance, reduced drinking, and fewer alcohol-related problems.

RECOMMENDATIONS FOR FUTURE RESEARCH

Much of the research on methods to increase disulfiram compliance has suffered serious flaws in research design, such as failure to adequately measure alcohol consumption and extent of compliance with disulfiram, failure to include appropriate control groups, noncomparable followup periods between experimental groups, failure to specify characteristics of individuals who respond to the compliance strategy and those who do not, and omission of reports on changes in drinking status following discontinuation of disulfiram. Further, inadequate attention has generally been given to the counseling or behavioral intervention received by patients, including the degree to which disulfiram and the compliance procedures were incorporated into the treatment. Resolution of these methodological concerns should characterize future research.

The authors repeat here and expand upon recommendations for specific research in disulfiram compliance that were offered in an earlier paper (Allen and Litten 1992). First, at the most fundamental level it is important to distinguish the contributions of medication compliance and the pharmacological activity of disulfiram. A double-blind 2 x 2 repeated measures design would be helpful in separating these two components. Factors would be disulfiram level (clinical versus nominal dose) and compliance enhancement (present versus absent). Analysis of variance would then allow these two main effects to be contrasted and would allow their interaction effects to be explained. Beyond issues of possible pharmacological effects of disulfiram, questions of research interest concern the relative effectiveness of supervised disulfiram versus unsupervised disulfiram versus no disulfiram in combination with the major forms of counseling (BMT, CRA, traditional 12-step disease model) used with disulfiram in prior research. The type of counseling received by subjects should be clearly specified and standardized. Another important question concerns the relative effectiveness and

patient retention with the simpler supervised disulfiram (e.g., Chick et al. 1992) versus the more complex BMT and CRA disulfiram contracts.

In future studies, alcohol consumption should be measured during and following the period of disulfiram administration. The postmeasures performed at the end of the intervention and throughout followup points also are quite important since the major benefit of disulfiram is believed to be sustained long-term sobriety. A convergent validity approach to measurement of compliance that includes biological measures (e.g., riboflavin as a urinary marker of compliance as in Fuller et al. 1986) and patient and collateral report of compliance is recommended to yield more accurate and complete data than reliance on a single indicator of compliance.

Second, investigations are needed to distinguish disulfiram volunteers who consistently take the drug from those who do not. Identification of characteristics of the noncompliant might provide important clues on more effective enhancement strategies. Third, while research on differential effectiveness of alternative treatment interventions with various subtypes of alcoholic patients has recently expanded (National Academy of Sciences 1990; National Institute on Alcohol Abuse and Alcoholism 1990), no patient-treatment matching studies with disulfiram as the intervention appear to have been conducted. Since disulfiram has been touted as a "chemical time-delay device" (Azrin 1976), it is possible to predict that impulsive drinkers, for example, might respond particularly well to it.

Fourth, minimal duration of disulfiram compliance to achieve long-term alcoholism treatment benefits should be determined. To date, most investigations on disulfiram compliance techniques have considered relatively short periods (generally 6 months or less). Perhaps there is some minimal time period needed for disulfiram assurance to establish a "disulfiram habit" in the patient. Following formation of a disulfiram habit, it is possible that patients would readily continue disulfiram even without external prompts (e.g., monitoring or incentives). Beyond this, there is the question of how long alcoholic patients should take disulfiram to achieve long-term stable sobriety. Fifth, externally imposed techniques to assure disulfiram compliance probably become quite burdensome for patients and those who monitor disulfiram ingestion. It would be helpful to develop and test "fading" procedures for disulfiram compliance strategies. Fading procedures might include less frequent monitoring and moving the patient to self-reinforce the use of disulfiram.

Lastly, a number of additional research questions focus on problems of acceptance of disulfiram by both patients and clinical staff in alcoholism treatment centers. In terms of patients, perhaps the most efficient way of enhancing disulfiram compliance will ultimately prove to be more convincing instructions on how disulfiram may benefit them and credibly showing them the relationship of disulfiram to their overall treatment plan. The disulfiram contracts used in BMT and CRA may be successful, at least in part, because they are integral to the entire treatment regime. Unfortunately, no research has as yet reported how varying instructional sets relate to voluntary disulfiram compliance.

In terms of staff acceptance of disulfiram, other issues seem paramount. Concerns about possible side effects and adverse reactions coupled with lack of familiarity on the part of physicians and treatment providers likely reduce utilization of disulfiram. Widely accepted guidelines for use of disulfiram that include recommended dosage, contraindications, and medical laboratory testing needed could facilitate its use by health care professionals. Another concern among some providers is that patients may see disulfiram as a panacea and refrain from seeking other treatments to reinforce commitment to long-term sobriety. The fear is that drinking will increase rapidly once disulfiram is stopped if patients have not developed the skills and motivation necessary for continued abstinence. The suggestion (Chick et al. 1992) that general practitioners might arrange for the spouse or a practice nurse supervising treatment to monitor disulfiram compliance would alarm many alcoholism treatment providers in the United States. Although the need for additional counseling beyond supervised disulfiram is ultimately an empirical question, guidelines recommending the use of disulfiram with counseling and instructions to providers on how to integrate disulfiram with ongoing counseling could be very helpful. A final concern among some providers is that supervised disulfiram might contribute to destructive patterns of relating in alcoholics' families. Implicit in this is an assumption that the alcoholic may resent the spouse or other family member who observes disulfiram ingestion and that the patient and/or spouse will assume that the spouse is responsible for sobriety maintenance. Such coercive family behavior coupled with tendencies by the alcoholic to avoid responsibility are thought to exacerbate the family member's emotional distress and reduce the alcoholic's chance of staying sober (O'Farrell 1993b). Both the BMT and CRA forms of the disulfiram contract include elements that address this concern, although simpler forms of supervised disulfiram do not.

Disulfiram, even with compliance assured, is likely to prove simply one helpful component to alcoholism treatment. Further, the authors strongly agree with Heather (1989) that a "large, properly designed treatment trial comparing supervised with unsupervised use of disulfiram" is needed. Research studies to distinguish benefits deriving from disulfiram and those deriving from the compliance strategy; determining the relative effectiveness of supervised versus unsupervised versus no disulfiram in combination with the major forms of counseling (BMT, CRA, traditional) used with disulfiram in prior research; identifying patients who respond most favorably to disulfiram; and discovering what types of compliance procedures-for example, simple, observed disulfiram as opposed to more comprehensive BMT and CRA disulfiram contracts-perform best and most efficiently are strongly encouraged.

REFERENCES

Allen, J.P., and Litten, R.Z. Techniques to enhance compliance with disulfiram. *Alcohol Clin Exp Res* 16:1035-1041, 1992.

Azrin, N.H. Improvements in the community-reinforcement approach to alcoholism. *Behav Res Ther* 14:339-348, 1976.

Azrin, N.H.; Sisson, R.W.; Meyers, R.; and Godley, M. Alcoholism treatment by disulfiram and community-reinforcement therapy. *J Behav Ther Exp Psychiatry* 13:105-112, 1982.

Bickel, W.K.; Rizzuto, P.; Zielony, R.D.; Klobas, J.; Panglosonlis, P.; Memiy, R.; and Knight, W.F. Combined behavioral and pharmacological treatment of alcoholic methadone patients. *J Subst Abuse* 1:161-171, 1989.

Bigelow, G.; Strickler, D.; Liebson, I.; and Griffiths, R. Maintaining disulfiram ingestion among outpatient alcoholics: A security-deposit contingency contracting procedure. *Behav Res Ther* 14:378-381, 1976.

Boume, P.G.; Alford, J.A.; and Bowcock, J.Z. Treatment of skid-row alcoholics with disulfiram. *J Stud Alcohol* 27:42-48, 1966.

Brewer, C., and Smith, J. Probation linked supervised disulfiram in the treatment of habitual drunken offenders: Results of a pilot study. Br Med J 287: 1282-1283, 1983.

Chick, J.; Gough, K.; Falkowski, W.; Kershaw, P.; Hore, B.; Mehta, B.; Ritson, B.; Ropner, R.; and Torley, D. Disulfiram treatment of alcoholism. *Br J Psychiatry* 161:84-89, 1992.

Cutter, H.S.G.; O'Farrell, T.J.; Choquette, K.A.; Brown, E.D.; and McCourt, W.F. "Couples Relapse Prevention Sessions after Behavioral Marital Therapy for Alcoholics and Their Wives: Outcomes During Three Years after Starting Treatment." Paper presented at the Annual Convention of the Association for the Advancement of Behavior Therapy, Atlanta, November 21, 1993.

Duckert, F., and Johnsen, J. Behavioral use of disulfiram in the treatment of problem drinking. *Int J Addict* 22:445-454, 1987.

Fuller, R.K.; Branchey, L.; Brightwell, D.R.; Derman, R.M.; Emrick, C.D.; Iber, F.K.; James, K.E.; Lacoursiere, R.B.; Lee, K.K.; Lowenstam, I.; Maany, I.; Neiderhiser, D.; Nocks, J.J.; and Shaw, S. Disulfiram treatment of alcoholism: A Veterans Administration Cooperative Study. *JAMA* 256:1449-1455, 1986.

Gerrein, J.R.; Rosenberg, CM.; and Manohar, V. Disulfiram maintenance in outpatient treatment of alcoholism. *Arch Gen Psychiatry* 28:798-802, 1973.

Heather, N. Disulfiram treatment for alcoholism. *Br Med J* 299:471-472, 1989.

Helzer, J.E.; Burnham, A.; and McEvoy, L.T. Alcohol abuse and dependence. In: Robins, L.N., and Regier, D.A., eds. *Psychiatric Disorders in America: The Epidemiologic Catchrnent Area Study.* New York: Free Press, 1991.

Hunt, G.M., and Azrin, N.H. A community-reinforcement approach to alcoholism. *Behav Res Ther* 11:91-104, 1973.

Johnsen, J.; Stowell, A.; Stensrud, T.; Ripel, A.; and Morland, J. A double-blind placebo controlled study of healthy volunteers given a subcutaneous disulfiram implantation. *Pharmacol Toxicol* 66:227-230, 1990.

Keane, T.M.; Foy, D.W.; Nunn, B.; and Rychtarik, R.G. Spouse contracting to increase Antabuse compliance in alcoholic veterans. *J Clin Psychol* 40:340-344, 1984.

Kofoed, L.L. Chemical monitoring of disulfiram compliance: A study of alcoholic outpatients. *Alcohol Clin Exp Res* 11:481-485, 1987.

Liebson, I.; Bigelow, G.; and Flamer, R.C. Alcoholism among methadone patients: A specific treatment method. *Am J Psychiatry* 130:483-485, 1973.

Liebson, I.A.; Tommasello, A.; and Bigelow, G.E. A behavioral treatment of alcoholic methadone patients. *Ann Intern Med* 89:342-344, 1978.

Miller, P.M. *Behavioral Treatment of Alcoholism.* New York: Pergamon Press, 1976.

Miller, P.M., and Hersen, M. "Modification of Marital Interaction Patterns Between an Alcoholic and His Wife." Jackson, MS: University of Mississippi Medical Center, 1975.

National Academy of Sciences; Institute of Medicine. *Broadening the Base of Treatment for Alcohol Problems.* Washington, DC: National Academy Press, 1990.

National Institute on Alcohol Abuse and Alcoholism. *Alcohol and Health.* Seventh Special Report to the U.S. Congress. DHHS Publication No. (ADM)90-1656. Washington, DC: Supt. of Docs., U.S. Govt. Print Off., 1990.

O'Farrell, T.J. A behavioral marital therapy couples group program for alcoholics and their spouses. In: O'Farrell, T.J., ed. *Treating Alcohol Problems: Marital and Family Interventions.* New York: Guilford Press, 1993a.

O'Farrell, T.J., ed. *Treating Alcohol Problems: Marital and Family Interventions.* New York: Guilford, 1993b.

O'Farrell, T.J., and Bayog, R.D. Antabuse contracts for married alcoholics and their spouses: A method to insure Antabuse taking and decrease conflict about alcohol. *J Subst Abuse Treat* 3:1-8, 1986.

O'Farrell, T.J.; Choquette, K.A.; Cutter, H.S.G.; Brown, E.D.; and McCourt, W.F. Behavioral marital therapy with and without additional relapse prevention sessions for alcoholics and their wives. *J Stud Alcohol* 54:652-666, 1993.

O'Farrell, T.J.; Cutter, H.S.G.; Choquette, K.A.; Floyd, F.J.; and Bayog, R.D. Behavioral marital therapy for male alcoholics: Marital and drinking adjustment during the two years after treatment. *Behav Ther* 23:529-549, 1992.

O'Farrell, T.J.; Cutter, H.S.G.; and Floyd, F.J. Evaluating behavioral marital therapy for male alcoholics: Effects on marital adjustment and communication from before to after therapy. *Behav Ther* 16:147-167, 1985.

Robichaud, C.; Strickler, D.; Bigelow, G.; and Liebson, I. Disulfiram maintenance employee alcoholism treatment: A three-phase evaluation. *Behav Res Ther* 17:618-621, 1979.

Sereny, G.; Sharma, V., Holt, J.; and Gordis, E. Mandatory supervised Antabuse therapy in an outpatient alcoholism program: A pilot study. *Alcohol Clin Exp Res* 10:290-292, 1986.

Wilson, A.; Blanchard, R.; Davidson, W.; McRae, L.; and Maini, K. Disulfiram implantation: A dose response trial. *J Clin Psychiatry* 45:242-247, 1984.

World Health Organization: Alcohol-Related Disabilities. WHO Offset Publication No. 32. Geneva: World Health Organization, 1977,

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Combining Behavioral Therapy and Pharmacotherapy for Smoking Cessation: An Update

John R. Hughes

INTRODUCTION

The purpose of this chapter is to update a prior review on the efficacy of combining behavioral therapy and nicotine replacement for smoking cessation (Hughes 1991). Specifically, this chapter will review five areas: (1) how the current zeitgeist for smoking research and treatment differs from that of traditional drug dependence, (2) major methodological issues in assessing combined psychological and pharmacological treatments, (3) efficacy of combined behavioral and nicotine replacement for smoking cessation, (4) possible behavioral mechanisms for the improved efficacy of combined treatments, and (5) the importance of nonefficacy outcomes in assessing combined therapy. (Note that the term behavioral treatments will be used in this chapter to encompass true structured behavioral treatments and treatments that have behavioral elements; e.g., most group therapies for smoking cessation include both behavioral and supportive therapy elements. Also, the term "drug abuse" will refer to nonnicotine, nonalcohol drug dependence or abuse.)

RESEARCH AND TREATMENT TRADITIONS OF NICOTINE VERSUS OTHER DRUG DEPENDENCIES

A brief history of research on and treatment of smoking can help understand why its traditions differ so much from those of other drugs of abuse (Lichtenstein and Glasgow 1992; Shiffman 1993). Early research on smoking treatment was limited to a few studies of various medications and studies of group education sessions. In the 1960s, psychologists successfully developed behavioral treatments such as aversive conditioning, contingency contracting, rapid smoking, self-monitoring, stimulus control, and relapse prevention (Shiffman 1993). Many studies showed these techniques increased abstinence rates from 20 to 40 percent. (All abstinence rates quoted in this chapter are for 1-year followup unless otherwise noted.)

Despite this success, many became disenchanted with behavior therapy because of the large financial and labor costs it would take to offer behavior therapy to all 50 million smokers in the United States alone (Chapman 1985). In addition, among smokers trying to stop, less than 7 percent have been willing to attend behavior therapy (Hughes 1993a). Thus, research focused next on briefer interventions such as self-help materials and physician advice. These showed modest effects; i.e., 5 to 15 percent of those treated abstained (Lichtenstein and Glasgow 1992). The utility of these brief interventions was questioned because so many smokers were stopping on their own due to the social and public health pressure in the 1980s.

At this same time, a general recognition of smoking as a drug dependence disorder became codified (American Psychiatric Association 1987; U.S. Department of Health and Human Services 1988), and a belief arose that those who were not quitting despite the intense social pressure were the more nicotine-dependent smokers (Coambs et al. 1989, pp. 337-348; Hughes 1993a). In 1984, nicotine polacrilex (nicotine gum) was marketed in the United States as the first proven antismoking medication followed soon after by transdermal nicotine (nicotine patch) (Hughes, in press). Because of the huge pool of smokers, these products were financial successes, and pharmaceutical companies became very interested in antismoking medications.

In contrast, research in and treatment of alcohol and drug dependence in the last 20 years has differed from smoking in several aspects (table 1). For example, in the United States, alcoholism treatment has been dominated by the disease model and 12-step traditions (Miller and Hester 1986, pp. 121-174). Interestingly, several behavioral interventions, brief interventions (e.g., bibliotherapy and physician advice), and some pharmacotherapies have been shown to improve outcomes, but these validated treatments have not been integrated into mainstream alcoholism therapy (Miller and Hester 1986, pp. 121-174). In summary, smoking treatment has been dominated by the necessity of clinical research demonstrating efficacy and by concern over cost-efficacy, whereas alcohol treatment has been dominated by allegiance to certain models of etiology and treatment.

One other comment about smoking versus alcohol and drug abuse research bears mentioning. Those who do research in alcohol and drug abuse rarely cite findings or methodologies of research in smoking and

TABLE 1. *Differences in emphusis in research on and treatment of nicotine, alcohol, and drug dependencies.* *

	Nicotine Dependence	Alcohol Dependence	Drug Dependence
Most accepted etiology	Behavioristic	Disease model	Pharmacological
Typical subjects	Few social problems, compliant	Interpersonal problems, noncompliant	Multiple problems, noncompliant
Psychiatric co-morbidity	Little interest by researchers	Depression, anxiety, antisocial	Antisocial personality
Common research methods	Large trials, long followup	Moderate-size trials, intermediate followup	Small trials, shorter followup
Most common psychological treatment	Group behavior therapy	12-step therapy	Counseling, group therapy
Most common pharmacological treatment	Replacement	Disulfiram	Replacement
Brief interventions	Much interest	Some interest	Little interest
Major mode of treatment delivery	Public organizations, primary care	Private clinics	Federal/State funded clinics
Major outcome	Biochemical-verified continuous abstinence	Observer-verified abstinence, functional improvement	Clean urines, functional improvement

NOTE: * These are the author's subjective impressions of reading the literature and of conducting research and clinical practice in these areas.

vice versa. This suggests researchers in one area are either unaware of findings in another or do not believe these findings are relevant. Those who do research in alcohol and drug abuse can learn about relapse curves, sophisticated data analyses, public health concerns, cost-efficacy, and so forth by reading the smoking literature. Conversely, those who do research in smoking can learn about assessing functional status, psychiatric co-morbidity, improving treatment retention, and so forth, by reading the alcohol and drug abuse literature.

EFFICACY OF NICOTINE REPLACEMENT IN THE ABSENCE OF BEHAVIOR THERAPY

Traditionally, an adjunctive psychological treatment has been thought to be essential for pharmacotherapy for drug abuse to be effective. However, many have hypothesized that since most smokers do not have as severe psychological problems as alcohol, cocaine, and heroin abusers, that perhaps pharmacotherapy in the absence of a psychological therapy would be effective in smokers (Hughes 1993a; Jarvis 1988, pp. 145-162).

Early conclusions by this author (Hughes 1986) and others (Lam et al. 1987) that nicotine polacrilex is only effective when given with behavior therapy appear to have been incorrect. Several recent meta-analyses have examined nicotine polacrilex and transdermal nicotine with and without behavioral therapy (Baillie et al. 1994; Cepeda-Benito 1993; Fiore et al. 1994a; Gourlay and McNeil 1990; Lam et al. 1987; Silagy et al. 1994; Tang et al. 1994) (table 2). Before discussing the results of these meta-analyses, two points need to be made. First, methodological procedures such as subject selection and type of control group have a profound effect on the absolute abstinence rates; thus, the fairest comparative measure in these meta-analyses is the odds ratio; i.e., the *relative* increase in quitting with nicotine polacrilex over a placebo or no-drug comparison group. Second, most studies did not adequately describe the contents of either the behavioral or pharmacological therapy; e.g., what behavioral techniques were used or how much medication was given for how long (Hughes 1991).

The four meta-analyses of *nicotine polacrilex* without behavior therapy reported odds ratios favoring nicotine polacrilex of 1.4, 1.5, 1.8, and 2.1 (first column, table 2). However, the absolute difference in quit rates with nicotine polacrilex is small; i.e., 0 percent to +7 percent (second column, table 2). In contrast, the three meta-analyses of the efficacy of

TABLE 2. *Meta-analysis of long-term quit rate with nicotine polacrilex (NP) or transdermal nicotine (TN) versus placebo with and without psychological therapy (PT).*

	NP				TN			
	No PT		PT		No PT		PT	
	OR	Δ%	OR	Δ%	OR	Δ%	OR	Δ
Baillie et al. (1994)	2.1	+7%	1.7	+10%				
Cepeda-Benito (1993)		+2%		+15%				
Fiore et al. (1994a)					2.5	+12%	3.4	+13%
Gourlay and McNeil (1990)	1.5		1.7					
Hughes (1991)		+4%		+7%				
Hughes (1993a)	1.4		2.1		2.6		2.4	
Lam et al. (1987)		0		+9%				
Silagy et al. (1994)	1.8	+5%	1.4	+8%	2.1	+10%	2	+10%
Tang et al. (1994)		+3%		+11%				

KEY: OR = odds ratio; A% = percent change.

transdermal nicotine without behavior therapy reported higher odds ratios of 2.1, 2.5, and 2.1 (fifth column, table 2) and more substantial increases in quit rates of +10 percent and +12 percent (sixth column, table 2).

To summarize, in contrast to pharmacotherapies for alcohol and illicit drug abuse, pharmacotherapy for smoking cessation (especially transdermal nicotine) is effective even when given without a structured psychological therapy.

EFFICACY OF ADDING NICOTINE REPLACEMENT TO BEHAVIOR THERAPY

Four meta-analyses have presented data that can estimate the effect of adding *nicotine polacrilex* to behavior therapy (third column, table 2). In these four meta-analyses, the odds ratio for long-term abstinence with adding nicotine polacrilex were 1.4, 1.7, 2.1, and 2.7, and absolute quit rates increased from +7 percent to +15 percent. Three meta-analyses have estimated the effect of adding *transdermal nicotine* to behavior therapy (next-to-last column, table 2). The reported odds ratios were 2.0, 2.4, and 3.4, and the increase in absolute quit rates was +10 percent and + 13 percent.

Cross-study comparisons (as in table 2) are always risky. However, one review examined several studies in which subjects were randomly assigned to receive or not receive behavior therapy and/or nicotine polacrilex (Hughes 1991). Thus, these were direct experimental tests of the efficacy of adding nicotine polacrilex. In fact, these factorial studies crossed the presence versus absence of pharmacotherapy with the presence versus absence of behavior therapy all within the same pool of subjects (figure 1).

The relative increase in cessation with adding nicotine polacrilex in these direct tests was 1.0, 1.3, 1.6, 1.7, 1.7, 1.8, and 2.5, with increases in cessation rates of 0 percent to +20 percent. Similar factorial studies with transdermal nicotine have not been reported. To summarize, adding

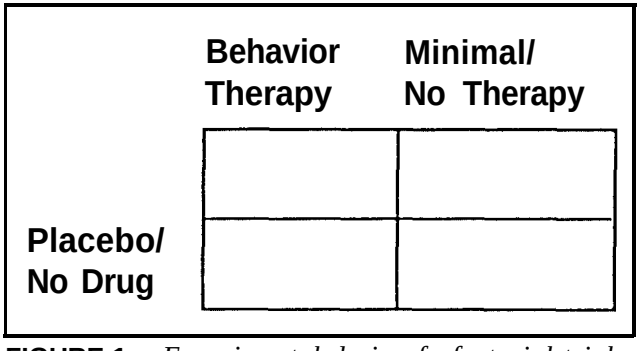

FIGURE 1. *Experimental design forfactorial trial of combining behavior therapy and drug therapy.*

nicotine gum or nicotine patch appears to double quit rates over those obtained with behavior therapy alone.

EFFICACY OF ADDING BEHAVIOR THERAPY TO NICOTINE REPLACEMENT

The converse question is how much quit rates would improve if behavior therapy was added to nicotine replacement. In terms of cross-study comparisons, none of the meta-analyses directly examined the efficacy of adding behavior therapy. However, two meta-analyses reported pooled quit rates with and without behavior therapy. Comparison of these rates indicates a +13 percent increase with adding behavior therapy to nicotine polacrilex (Silagy et al. 1994) and a +7 percent and +6 percent increase with adding behavior therapy to transdermal nicotine (Fiore et al. 1994a).

In the previously mentioned review of direct tests (Hughes 1991), the odds ratios for adding behavioral therapy to nicotine polacrilex were 0.8, 1.0, 1.6, 1.7, 1.7, 1.8, and 2.5, and absolute increases in quit rates were 0 percent to +27 percent. Since that review, one other study has reported data that, when recalculated, produces an odds ratio of 2.7 (Goldstein et al. 1989).

In terms of direct tests of adding psychological therapy to transdermal nicotine, this author is aware of only one randomized study (Buchkremer et al. 1991). That study examined adding training in relapse-coping strategies with and without booster sessions and found no increased efficacy with adding behavior therapy. One other article compared two studies of transdermal nicotine in which subjects received group behavioral therapy in one but little therapy in the other (Fiore et al. 1994b). Although subjects were not randomized to groups, they were recruited in a similar manner, the drug treatment was similar, and the outcomes were similarly defined. Comparison of the results of these two studies indicates an odds ratio of 3.1 for adding behavior therapy to transdermal nicotine. To summarize, the bulk of the evidence suggests adding behavior therapy to nicotine replacement approximately doubles quit rates over using nicotine replacement alone.

COMBINED THERAPY USING OTHER THERAPIES

The only other smoking cessation medication with a substantial database is clonidine. One meta-analysis reported an odds ratio for adding clonidine to behavior therapy of 4.2 (Covey and Glassman 1991). No data were available for adding behavior therapy to clonidine. Although this result suggests clonidine is a very effective drug at potentiating behavior therapy, many of the studies reviewed in this meta-analysis had only short-term outcomes and were published in abstract forms (Hughes, in press). As importantly, more recent articles have not replicated these effects (Glassman et al. 1993; Gourlay et al. 1994; Prochazka et al. 1992).

One other study done several years ago examined combining a non-nicotine pharmacological treatment and psychological treatments (Schwartz and Dubitsky 1967, 1968). This study was essentially a 3x3 factorial contrasting tranquilizers, placebo, and no-drug conditions with group therapy, individual therapy, and no-contact conditions. The psychological therapies were effective but the tranquilizers were not; thus, combined therapy was not any better than group or individual therapy alone.

One other study examined adding different types of psychological therapies (Hajek et al. 1985). Adding traditional group therapy to nicotine polacrilex improved outcome with nicotine polacrilex more than adding didactic, therapist-oriented group therapy (28 percent versus 17 percent). Replications of this finding have yet to be published.

BEHAVIORAL MECHANISMS TO EXPLAIN INTERACTIONS OF BEHAVIOR AND PHARMACOLOGICAL TREATMENTS

Behavioral Mechanisms to Explain Negative Interactions

Attribution theory (Davison and Valin 1969) hypothesizes that if smokers attribute their success to medications, then without medication they should expect to relapse. State-dependent learning (Whitehead and Blackwell 1979, pp. 157-189) hypothesizes that relapse-prevention skills learned while on medication will not be remembered when smokers are off medication and, thus, smokers will relapse after stopping medications. In contrast to these theories, there is no evidence that relapse rates are greater after recommended or forced cessation of nicotine gum than

during the comparable period for no-drug or placebo groups (Fiore et al. 1994a; Hughes 1993a; Sachs et al. 1994; Silagy et al. 1994).

COMPLEMENTARY EFFECTS ACROSS MEDIATING VARIABLES

One description of why stopping smoking can be so difficult is that it requires trying to make major behavioral and environmental changes while at the same time suffering from withdrawal symptoms of difficulty concentrating, irritability, insomnia, etc. Thus, the positive effect of combined therapy could be because behavior therapy improves behavioral skills and nicotine replacement improves withdrawal. Interestingly, although nicotine replacement has been shown to decrease withdrawal (Hughes et al. 1990, pp. 317-398), whether this is the mechanism of its efficacy is suspect, because, surprisingly, the severity of withdrawal is only minimally related to the ability to abstain (Hughes and Hatsukami 1992; West, in press). Similarly, whether behavior treatments actually change behaviors that are linked to the ability to abstain is (surprisingly) unknown (Payne et al. 1990).

COMPLEMENTARY EFFECTS ACROSS TIME

A related explanation for the efficacy of combined therapy is that nicotine replacement helps smokers stop in the first few weeks (when withdrawal is at its worst), and then behavioral therapy kicks in to help smokers stay stopped (since it may take a few weeks to learn the behavioral skills). If this were true then in a factorial experiment one would expect the behavior-therapy-only group to have higher relapse initially but lower relapse later; the pharmacotherapy-only group to have lower relapse initially and greater relapse later; the untreated control group to have high relapse both early and late; and the combined treatment to have low relapse both early and late (figure 2). One study did report less later relapse with behavior therapy (Goldstein et al. 1989). However, the expected pattern illustrated in figure 2 was not seen among the seven factorial studies with nicotine polacrilex (Hughes 1991); e.g., the nicotine polacrilex only group did not have high relapse rates after stopping nicotine polacrilex and the behavior therapy groups did not have less relapse between 3- and 12-month followup. Also, the pattern of relapse in studies of nicotine patches without behavior therapy is similar to that

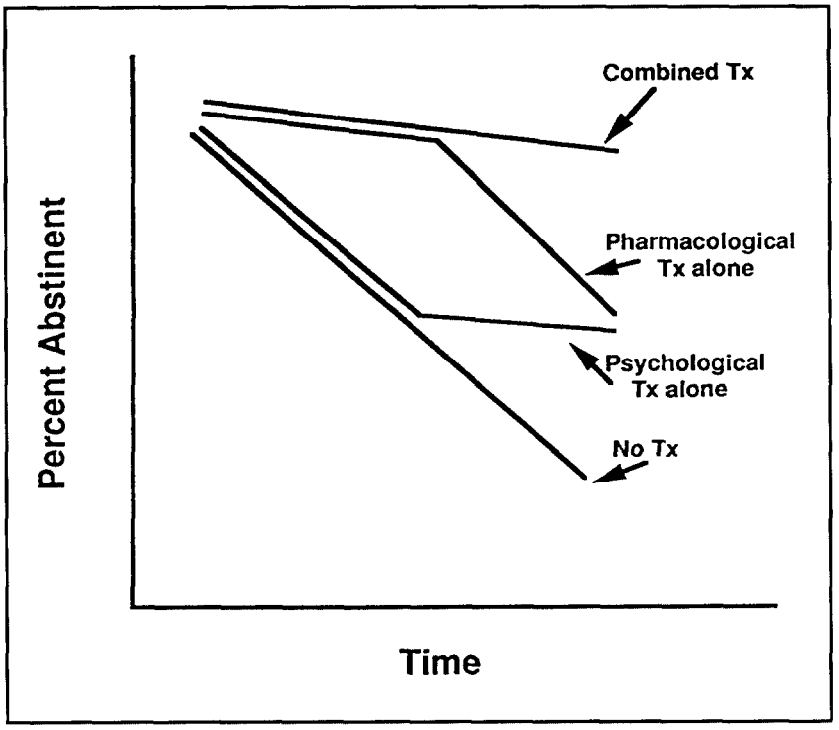

FIGURE 2. *Expected outcome if behavior therapy and pharmacotherapy worked at different times.*

of studies of nicotine patches with behavior therapy (Fiore et al. 1994a; Sachs et al. 1994; Silagy et al. 1994).

COMPLEMENTARY EFFECTS ACROSS SUBJECTS

Another related explanation for increased quit rates with combined therapy is that behavior therapy and pharmacological therapy are helping two different groups of smokers. The large majority of studies have found that nicotine polacrilex is especially helpful to the more dependent smoker (Fagerstrom and Schneider 1989); however, for unknown reasons, it is not a robust predictor of benefit from transdermal nicotine (Fiore et al. 1994a; Hughes 1993a). In addition, predictors of benefit from behavior treatments for smoking have not been identified (Fiore et al. 1994a; Hughes 1993a). Finally, the subgroups of responders to behavior and to psychological therapy may not be orthogonal; e.g.,

dependent smokers may also especially need behavior therapy and smokers who do not need pharmacotherapy may not need behavior therapy as well.

ONE THERAPY INCREASES COMPLIANCE WITH THE OTHER

Pharmacotherapy may decrease distracting symptoms of irritability, difficulty concentrating, and so forth, such that smokers are more able to comply with behavioral skills training. Conversely, behavior therapy may provide increased motivation, which translates to improved compliance with the pharmacotherapy. Unfortunately, few studies reported compliance across groups. Two studies did report greater attendance at behavior therapy in groups that also received nicotine gum versus groups that did not receive gum, but one study reported similar use of gum in behavior therapy and no therapy groups (Hughes 1991). No studies reported attendance at behavior therapy as a function of drug group (Hughes 1991).

NONEFFICACY OUTCOMES

Efficacy (i.e., the increase in abstinence rates in a given study) is but one measure of treatment utility (Hollon and Beck 1987, pp. 437-490). Other measures are acceptability, availability, cost-efficacy, side-effect profile, and universality. The *acceptability* of behavior therapy for smoking cessation appears very poor, as less than 7 percent of smokers will attend free psychological therapy (Hughes 1993a). This may be due to poor availability (see below), nonreimbursement, or the general view that although talking therapy is often needed to overcome alcohol problems, this is not true for smoking. The acceptability of pharmacotherapy; e.g., how often smokers fill physician-initiated prescriptions for nicotine replacement, is unknown. Psychiatrists often use pharmacotherapy initially to engage a patient in treatment and then turn to psychotherapy (Hughes and Pierattini 1992, pp. 97-126). Whether combining pharmacological and behavior treatments for smoking would make either treatment more acceptable is unknown.

The *availability* of psychological therapy for smoking cessation often is very poor. The most widely available treatments are those by public organizations such as the American Cancer Society, the American Heart Association, the American Lung Association, the Seventh-Day

Adventists, or hospital/clinic programs. Often these are not available in rural areas, and even in urban areas programs often occur only 2 or 3 times a year. Thus, to avail themselves of this treatment, many smokers would have to wait for long periods and drive many miles to attend the treatments. The availability of pharmacotherapy may appear high considering the large number of prescriptions that are filled. However, surprisingly few primary care physicians prescribe nicotine replacement appropriately (Cummings et al. 1988; U.S. Department of Health and Human Services 1988), and specialists in smoking cessation are not likely to arise given the lack of reimbursement from health insurance. Thus, the availability of adequate pharmacotherapy also appears limited. In terms of combined therapy, many withdrawal clinics either ignore or discourage use of pharmacological treatments (Hughes 1986, pp. 141-147), and many physicians do not refer to behavioral treatments (Cummings et al. 1988; U.S. Department of Health and Human Services 1988); thus, combined treatment is probably even less available to the large majority of smokers.

The *cost-efficacy* of brief treatments for smoking cessation is so much greater than that of all other medical interventions that it has been termed the gold standard for comparison (Tsevat 1992). The cost-efficacy of a course of nicotine replacement (Oster et al. 1986) and of intensive psychological therapy (Altman et al. 1987) also are quite good. The real question is whether adding a second treatment is cost-effective. To examine this, some cost estimates from another article (Hughes et al. 1991) and the quit rates for the seven factorial studies of nicotine gum (Hughes 1991) to estimate cost per quitter were used (tables 3 and 4). Although adding a second therapy increases quit rates, it does not do so to the extent that it prevents an escalation in cost per quitter. There are two ways to interpret this result. The first interpretation points to the increased cost per quitter with combined therapy and states that, until there are ways to determine who needs combined therapy, there should not be reimbursement for combined therapy for all comers. The second interpretation points out the large economic benefits of smoking cessation; e.g., the cost-benefit of a 40- to 45-year-old moderate smoker stopping is $19,329 (Oster et al. 1984). Since these benefits greatly exceed the cost of the combined treatment, then combined treatment could be justified for all comers. Although the above two arguments are overly simplistic (Warner 1987), they do illustrate the dilemma about cost-efficacy that combined treatments face.

TABLE 3. *Percent abstinent in meta-analysis of seven factorial studies of nicotine gum. **

	Psychological Treatment	Control Treatment
Nicotine	30	22
Control	23	18

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The side effects of nicotine replacement are well known and are benign (Hughes 1993b); e.g., less than 5 percent of those on transdermal nicotine drop out due to side effects (Hughes and Glaser 1993). Side effects from behavioral treatment have not been examined but are possible; e.g., a decreased probability of future quit attempts among those who fail.

Universality refers to whether a treatment can help a large group of persons with a disorder or only a small group; thus, this notion is closely tied to the proposed behavioral mechanism of complementary effects across subjects; i.e., more smokers are more likely to find something of benefit in a combined therapy than in a single therapy. As stated above, whether or not this is true for combined treatment of smoking is unclear.

TABLE 4. *Median cost per quitter across seven factorial studies of nicotine gum.*

	With Behavior Therapy	Without Behavioral Therapy
Nicotine	$1,060	$664
Control	$850	$343

CONCLUDING COMMENTS

The available data suggest combined behavioral and pharmacological therapy substantially increases smoking cessation over behavior therapy alone and over pharmacological therapy alone. However, there are many gaps in knowledge of the issue; e.g., how much does combined therapy increase outcome with transdermal nicotine and how does combined therapy increase quit rates? In this era of concern over health care costs, perhaps the more important issues are the cost-efficacy of combined therapy and the specification of which smokers need combined therapy and which can do well with behavioral therapy alone or with pharmacological therapy alone.

REFERENCES

Altman, D.G.; Flora, J.A.; Fortmann, S.P.; and Farquhar, J.W. The cost-effectiveness of three smoking cessation programs. *Am J Public Health* 77:162-165, 1987.

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 3d ed. rev. Washington, DC: American Psychiatric Association, 1987.

Baillie, A.; Mattick, R.P.; Hall, W.; and Webster, P. Meta-analytic review of the efficacy of smoking cessation interventions. *Drug Alcohol Rev* 13:179-192, 1994.

Buchkremer, G.; Minneker, E.; and Block, M. Smoking-cessation treatment combining transdermal nicotine substitution with behavioral therapy. *Pharmacopsychiatry* 24:96-102, 1991.

Cepeda-Benito, A. Meta-analytical review of the efficacy of nicotine chewing gum in smoking treatment programs. *J Consult Clin Psychol* 61:822-830, 1993.

Chapman, S. Stop-smoking clinics: A case for their abandonment. *Lancet* 1(8434):918-920, 1985.

Coambs, R.B.; Kozlowski, L.T.; and Ferrence, R.G. The future of tobacco use and smoking research. In: Ney, T., and Gale, A., eds. *Smoking and Human Behavior*. New York: John Wiley & Sons, Ltd., 1989.

Covey, L.S., and Glassman, A.H. A meta-analysis of double-blind placebo-controlled trials of clonidine for smoking cessation. *Br J Addict* 86:991-998, 1991.

Cummings, S.R.; Hansen, B.; Richard, R.J.; Stein, M.J.; and Coates, T.J. Internists and nicotine gum. *JAMA* 260: 1565-1569, 1988.

Davison, G.C., and Valin, S. Maintenance of self-attributed and drug-attributed behavior change. *J Pers Soc Psychol* 11:25-33, 1969.

Fagerstrom, K.O., and Schneider, N.G. Measuring nicotine dependence: A review of the Fagerstrom tolerance questionnaire. *J Behav Med* 12:159-182, 1989.

Fiore, M.C.; Kenford, S.L.; Jorenby, D.E.; Wetter, D.W.; Smith, S.S.; and Baker, T.B. Two studies of the clinical effectiveness of the nicotine patch with different counseling treatments. *Chest* 105:524-533, 19946.

Fiore, M.C.; Smith, S.S.; Jorenby, D.E.; and Baker, T.B. The effectiveness of the nicotine patch for smoking cessation: A meta-analysis. *JAMA* 271:1940-1946, 1994a.

Glassman, A.H.: Covey, L.S.; Dalack, G. W.; Stetner, F.; Rivelli, S.K.; Fleiss, J., and Cooper, T.B. Smoking cessation, clonidine, and vulnerability to nicotine among dependent smokers. *Clin Pharmacol Ther* 54:670-679, 1993.

Goldstein, M.G.; Niaura, R.; Follick, M.J.; and Abrams, D.B. Effects of behavioral skills training and schedule of nicotine gum administration on smoking cessation. *Am J Psychiatry* 146:56-60, 1989.

Gourlay, S.; Forbes, A.; Marriner, T.; Kutin, J.; and McNeil, J. A placebo-controlled study of three clonidine doses for smoking cessation. *Clin Pharmacol Ther* 55:64-69, 1994.

Gourlay, S.G., and McNeil, J.J. Antismoking products. *Med J Aust* 153:699-707, 1990.

Hajek, P.; Belcher, M.; and Stapleton, J. Enhancing the impact of groups: An evaluation of two group formats for smokers. *Br J Clin Psychol* 24:289-294, 1985.

Hollon, S.D., and Beck, A.T. Psychotherapy and drug therapy: Comparisons and combinations. In: Garfield, S.L. and Bergin, A.E., eds. *Handbook of Psychotherapy and Behavior Change.* New York: John Wiley and Sons, 1987.

Hughes, J.R. Problems of nicotine gum. In: Ockene, J.K., ed. *Pharmacologic Treatment of Tobacco Dependence: Proceedings of the World Congress, November* 3-5, 1985. Cambridge, MA: Institute for the Study of Smoking Behavior and Policy, 1986.

Hughes, J.R. Combined psychological and nicotine gum treatment for smoking: A critical review. *J Subst Abuse* 3:337-350, 1991.

Hughes, J.R. Pharmacotherapy for smoking cessation: Unvalidated assumptions and anomalies, and suggestions for further research. *J Consult Clin Psychol* 61:751-760, 1993a.

Hughes, J.R. Risk/benefit of nicotine replacement in smoking cessation. *Drug Saf* 8:49-56, 1993b.

Hughes, J.R. Nicotine dependence. In: Schuster, C.R.; Gust, S.W.; and Kuhar, M.J., eds. *Pharmacological Aspects of Drug Dependence: Toward an Integrative Neurobehavioral Approach: Handbook of Experimental Psychology Series.* New York: Springer-Verlag, in press.

Hughes, J.R., and Glaser, M. Transdermal nicotine for smoking cessation. *Health Values* 17:24-31, 1993.

Hughes, J.R., and Hatsukami, D.K. The nicotine withdrawal syndrome: A brief review and update. *Int J Smok Cessation* 1:21-26, 1992.

Hughes, J.R.; Higgins, S.T.; and Hatsukami, D.K. Effects of abstinence from tobacco: A critical review. In: Kozlowski, L.T.; Annis, H.; Cappell, H.D.; Glaser, F.; Goodstadt, M.; Israel, Y.; Kalant, H.; Sellers, E.M.; and Vingilis, J., eds. *Research Advances in Alcohol and Drug Problems.* Vol. 10. New York: Plenum Press, 1990.

Hughes, J.R., and Pierattini, R. Principles of pharmacotherapy for mental disorders. In: Grabowski, J., and Vandenbos, G.R., eds. *Psychopharmacology: Basic Mechanisms and Applied Interventions: 1991 Master Lectures in Psychology.* Washington, DC: American Psychological Association, 1992.

Hughes, J.R.; Wadland, W.C.; Fenwick, J. W.; Lewis, J.; and Bickel, W.K. Effect of cost on the self-administration and efficacy of nicotine gum: A preliminary study. *Prev Med* 20:486-496, 1991.

Jarvis, M. Nicotine replacement as sole therapy or as adjunct. In: Pomerleau, O.F.; Pomerleau, C.S.; Fagerstrom, K.O.; Henningfield, J.E.; and Hughes, J.R., eds. *Nicotine Replacement: A Critical Review.* New York: Alan R. Liss, 1988.

Lam, W.L.; Sze, P.C.; Sacks, H.S.; and Chalmer, T.C. Meta-analysis of randomized controlled trials of nicotine chewing gum. *Lancet* 2:27-29, 1987.

Lichtenstein, E., and Glasgow, R.E. Smoking cessation: What have we learned over the past decade? *J Consult Clin Psychol* 60:518-527, 1992.

Miller, W.R., and Hester, R.K. The effectiveness of alcoholism treatment: What research reveals. In: Miller, W.R., and Heather, N., eds. *Treating Addictive Behaviors: Processes of Change.* New York: Plenum Press, 1986.

Oster, G.; Colditz, G.A.; and Kelly, N.L. *The Economic Costs of Smoking and Benefits of Quitting.* Lexington, MA: D.C. Heath and Company, 1984.

Oster, G.; Huse, D.M.; Delea, T.E.; and Colditz, G.A. Cost-effectiveness of nicotine gum as an adjunct to physicians' advice against cigarette smoking. *JAMA* 256:1315-1318, 1986.

Payne, T.J.; Etscheidt, M.; and Corrigan, S.A. Conditioning arbitrary stimuli to cigarette smoke intake: A preliminary study. *J Subst Abuse* 2:113-119, 1990.

Prochazka, A.V.; Petty, T.L.; Nett, L.; Silvers, G.W.; Sachs, D.P.L.; Rennard, S.I.; Daughton, D.M.; Grimm, R.H., Jr.; and Heim, C. Transdermal clonidine reduced some withdrawal symptoms but did not increase smoking cessation. *Arch Int Med* 152:2065-2069, 1992.

Sachs, D.P.L.; Bostrom, A.G.; and Hansen, M.D. "Relapse Hazard Functions During and After Nicotine Patch Smoking Cessation Treatment." Abstract presented at the Society of Behavioral Medicine Meeting, Boston, April 12, 1994.

Schwartz, J.L., and Dubitsky, M. The smoking control research project: Purpose, design, and initial results. *Psychol Rep* 20:367-376, 1967.

Schwartz, J.L., and Dubitsky, M. One-year follow-up results of a smoking cessation program. *Can J Pub Health* 59:161-165, 1968.

Shiffman, S. Smoking cessation treatment: Any progress? *J Consult Clin Psychol* 61:718-722, 1993.

Silagy, C.; Mant, D.; Fowler, G.; and Lodge, M. The effectiveness of nicotine replacement therapies in smoking cessation. *Online J Curr Clin Trials* 113: [7,906 words; 110 paragraphs], 1994.

Tang, J.L.; Law, M.; and Wald, N. How effective is nicotine replacement therapy in helping people to stop smoking? *Br Med J* 308:21-25, 1994.

Tsevat, J. Impact and cost-effectiveness of smoking interventions. (Supplement 1 A). *Am J Med* 93:43S-47S, 1992.

U.S. Department of Health and Human Services. *The Health Consequences of Smoking: Nicotine Addiction: A Report of the U.S. Surgeon General.* Washington, DC: Supt. of Docs., U.S. Govt. Print. Off., 1988.

Warner, K.E. Health and economic implications of a tobacco-free society. *JAMA* 258:2080-2086, 1987.

West, R.J. The "nicotine replacement paradox" in smoking cessation: How does nicotine gum really work? *Br J Addict* 87:165-167, 1992.

Whitehead, W.E., and Blackwell, B. Interactions between drugs and behavior therapy. In: McNamara, J.R., ed. *Behavioral Approaches to Medicine.* New York: Plenum Press, 1979.

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Integrating Psychological and Pharmacological Treatment of Dually Diagnosed Patients

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INTRODUCTION

In the past decade, there has been substantially increased interest in patients with coexisting psychiatric illness and substance use disorders (Meyer 1986a; Minkoff and Drake 1991; Mirin 1984). Two main factors have contributed to the interest in this subject. First, studies of both primary substance abusers (Mirin et al. 1991; Ross et al. 1988; Rounsaville et al. 1991) and patients with primary psychiatric disorders (Caton et al. 1989; Drake and Wallach 1989; McLellan and Druley 1977) in clinical settings have revealed substantial rates of co-morbidity with the other disorder. Moreover, results of the National Institute of Mental Health Epidemiological Catchment Area study (Regier et al. 1990) confirmed that the frequent association between substance use disorders and psychiatric illness is not due to the bias inherent in studying clinical populations, but occurs in the general population at a significantly higher rate than would be expected by chance alone.

A second reason for the interest in these so-called "dually diagnosed" patients is the fact that research conducted in the early 1980s (McLellan et al. 1983) revealed that substance abusers with high levels of psychiatric severity (regardless of the exact nature of the specific coexisting psychiatric disorder) had poor treatment outcomes. In a series of studies by McLellan (1986, pp. 97-139), the level of psychiatric severity was the most robust predictor of treatment outcome in their population of alcohol and drug-dependent patients. Moreover, certain forms of traditional drug abuse treatment, such as the confrontational approach utilized in residential therapeutic communities (TCs), were found to be particularly ill-suited for patients with coexisting psychiatric illness, as demonstrated by the finding that such patients who were treated in TCs had worse outcomes with longer treatment.

The combined findings of high rates of co-morbidity and a growing recognition of the ineffectiveness of traditional forms of substance abuse

treatment for dually diagnosed patients has led clinicians and researchers in recent years to (a) characterize more clearly the relationship between substance abuse and psychiatric disorders, and (b) search for effective approaches to the treatment of this patient population.

THE RELATIONSHIP BETWEEN SUBSTANCE ABUSE AND PSYCHOPATHOLOGY

In treating a patient with a substance use disorder and coexisting psychiatric illness, it is important to understand the potential relationship between the patient's two disorders. Meyer (1986b) has described six different ways in which substance abuse and psychopathology may interrelate: (a) Axis I or Axis II disorders may act as risk factors for substance use disorders, (b) psychopathology may affect the course of a substance use disorder, (c) psychiatric symptoms may develop in the course of chronic intoxication, (d) chronic substance use may lead to the development of psychiatric disorders that do not remit despite cessation of substance use, (e) substance use and psychiatric symptoms may become meaningfully linked over time, and (f) the two disorders may coexist without being related to each other.

In addition to the multiple potential relationships between substance use disorders and psychiatric illness, it is important to recognize the multiplicity of clinical presentations that can be subsumed by the term "dually diagnosed" patient (Weiss et al. 1992a). For example, the nature, length, and severity of psychopathology and of the substance use disorder may vary widely. Dually diagnosed patients thus include a broad range of individuals, including patients with chronic severe mental illness and relatively mild substance use disorders, as well as patients with severe substance dependence and mild psychopathology, e.g., a simple phobia that is unrelated to the substance use. Moreover, even patients with the same two disorders, e.g., alcohol dependence and depression, may have different severity patterns based on a number of factors, including which disorder occurred initially (i.e., which disorder was "primary"). For example, Weissman and colleagues (1977) noted that patients with secondary depression and primary substance use disorder had less severe depressive symptoms than patients with primary mood disorder and secondary substance use disorder. This heterogeneity in patients who are dually diagnosed underscores the need to develop a variety of treatment approaches when working with this population.

GENERAL PRINCIPLES IN TREATING DUALLY DIAGNOSED PATIENTS

A number of studies (Kosten et al. 1987; McLellan et al. 1981) have shown that although patients with substance use disorders may have a wide range of problems associated with their addiction, these problems (including psychiatric problems) are not necessarily caused by their addictive disorder, and therefore do not necessarily improve merely as a result of achieving abstinence. Therefore, there has been increasing recognition that patients with coexisting substance use disorders and psychiatric illness need to receive treatment for both disorders, as well as for associated problems such as vocational, legal, medical, and interpersonal difficulties (McLellan et al. 1992, pp. 231-252). Although there are differences of opinion regarding which specific techniques to utilize in dual diagnosis treatment, several stages have commonly been described in the treatment of these patients: crisis intervention, medical and psychiatric stabilization, engagement, motivation or "persuasion" of the patient to seek substance abuse treatment, asking the patient to make a commitment to pursue active treatment, and relapse prevention (Fariello and Scheidt 1989; Kofoed and Keys 1988; Minkoff 1989; Ridgely 1991, pp. 29-42). Since both psychiatric illnesses (particularly those of greater severity) and addictive disorders are frequently accompanied by minimization or denial of symptoms, overcoming this resistance to treatment (which is frequently related to feelings of shame, stigma, and hopelessness) is an important early step in the treatment process.

There has been some controversy over whether the treatment of dually diagnosed patients should occur in an "integrated" or a "sequential" program (Minkoff 1989). Integrated treatment programs, which provide simultaneous substance abuse and psychiatric treatment, have recently gained favor (Minkoff 1989; Ries and Ellingson 1990), although the authors are aware of no studies that have clearly demonstrated the superiority of this approach over sequential treatment, in which dually diagnosed patients receive episodes of substance abuse treatment and psychiatric treatment in sequence (in either order, depending on the patient, program, or response to treatment).

Despite some fundamental differences in the integrated versus sequential models, one similarity between the approaches is the general use of pharmacotherapy to primarily treat the patient's psychiatric disorder (Siris 1990), with the implicit hope that improvement in psychiatric symptoms

will (a) help make a patient more accessible to psychosocial treatment for substance abuse, and (b) reduce the patient's vulnerability to relapse to substance use by diminishing symptoms such as psychosis, depression, or anxiety. Indeed, one of the problems with some of the early studies of antidepressant treatment of alcoholic patients was related to this implicit assumption. Indeed, some such studies failed to measure changes in both depression and drinking behavior as outcome measures (Ciraulo and Jaffe 1981). One of the advances in more recent clinical and research approaches to this topic has been the clear understanding that the treatment of dually diagnosed patients requires specific attention to both disorders, and measurement of outcome in both domains.

POTENTIAL EFFECTS OF COMBINING PSYCHOTHERAPY WITH PHARMACOTHERAPY

The integration of psychotherapeutic and pharmacologic approaches to psychiatric illnesses other than substance abuse has been the subject of a great deal of research (Beitman and Klerman 1991; Karasu 1982; Sarwer-Foner 1983, pp. 165-180). Klerman (1991, pp. 3-19) has outlined a number of potential interactional effects between pharmacologic treatment and psychotherapy. He has divided these into both positive and negative effects; the potential effects of pharmacotherapy on psychotherapy are listed in table 1.

Klerman (1991, pp. 3-19) also has described the potential beneficial and detrimental effects of psychotherapy on psychopharmacologic treatment. First, some individuals may hold the belief that since psychotropic drug treatment is designed to correct an underlying metabolic or biochemical imbalance or dysfunction, then adding psychotherapy (while not necessarily harmful) would represent an unnecessary investment in time, energy, and expense. Moreover, it is possible that exploratory psychotherapy, particularly when undertaken early in the treatment process, may disrupt early defenses and undo some of the healing and "sealing over" that is facilitated by the use of medications. It is important to note that these potential objections to psychotherapy are theoretical and not based on empirical studies that demonstrate the worsening of patients when psychotherapy is added to their pharmacotherapeutic regimen. Theoretical benefits to the addition of psychotherapy to medication treatment include (a) the facilitation of medication compliance by helping the patient to further understand the nature of his or her illness and

TABLE 1. *Potential positive and negative effects of pharmacologic treatment on psychotherapy.*

Positive Effects
1. Medications facilitate accessibility to psychotherapy.
2. Medications influence the ego-psychological functions (cognitive functioning, attention, verbal skills, concentration) required for participation in psychotherapy.
3. Medications may promote abreaction.
Negative Effects
1. Reduction of symptoms may lead patients to stop psychotherapy.
2. Medications may undercut defenses.
3. For patients who value psychotherapy, the use of medications may be seen as a failure on their part.

enhancing motivation for positive change; and (b) the correction of associated difficulties such as interpersonal problems and poor self-esteem, which may occur as a result of having a psychiatric illness. Patients with substance use disorders, even in the absence of associated psychopathology, are frequently noncompliant with medication regimens and suffer from poor self-esteem, shame, interpersonal difficulties, and a variety of other associated problems. It therefore could be posited that psychotherapeutic interventions with dually diagnosed patients, who experience these difficulties in a more profound way as the result of having more than one illness, would serve to both help improve compliance and to assist in the rehabilitative process. Since ensuring medication compliance is one of the primary treatment goals in working with psychiatric patients, and since dually diagnosed patients tend to have poorer medication compliance than either patients with substance use disorders alone or psychiatric illness alone (Drake et al. 1989), addressing this issue is critical.

TREATMENT OUTCOME STUDIES WITH DUALLY DIAGNOSED PATIENTS

Despite evidence from studies of both substance abusers and other psychiatric patients that a combination of psychotherapy and

pharmacotherapy is more effective than either alone, there have been virtually no studies of this subject in dually disordered patients. Rather, most treatment studies of patients with substance use disorders and coexisting mood or anxiety disorders have thus far involved trials of medications that are primarily designed to treat the coexisting psychiatric illness, with the hope that by carefully identifying and treating coexisting psychiatric disorders in substance abusers, the outcome of their substance use disorders can be improved as well. Studies of patients with psychotic and substance use disorders have, on the other hand, primarily focused on psychosocial strategies that integrate the treatment of the two disorders; the medications used are generally held constant and are typically those medications ordinarily prescribed for the treatment of psychosis.

DEPRESSION

A number of studies have examined the treatment of depressed substance abusers with antidepressants (Weiss and Mirin 1989). Despite the aforementioned methodological flaws of early antidepressant studies, more recent research has suggested the potential benefit of this treatment approach, at least for improving mood. Nunes and colleagues (1993) studied the efficacy of imipramine in patients with primary depression and alcoholism. They treated 60 such patients in a 12-week open-label trial; the 35 patients (58 percent) who were judged to be responders during this initial period (i.e., they had substantial improvement in both mood and drinking behavior), were then offered the opportunity to enter a double-blind, placebo-controlled, 6-month discontinuation trial. Twenty-six patients entered this phase of the study, 23 of whom completed the trial. Four of 13 patients (31 percent) relapsed on imipramine, as compared with 7 of 10 (70 percent) who relapsed on placebo ($p = 0.09$). The authors noted that in a subgroup of patients, imipramine had a more powerful effect on mood than on drinking. Moreover, patients with coexisting panic disorder appeared to have a more robust response to imipramine than did patients with depression alone.

A small study of desipramine for patients with depression secondary to alcoholism also suggested its potential utility. Mason and colleagues (1992) compared 11 patients on desipramine with 10 patients on placebo in a 6-month random assignment trial and found that patients treated with desipramine had significantly more sober days and significantly fewer depressive symptoms than patients who were given placebo.

Thus, recent studies of antidepressant treatment of coexisting depression and alcoholism suggest the possibility of a positive response, although the major benefit of this treatment approach may be the reduction of depressive symptoms. Although this is intrinsically helpful, mood improvement is not necessarily associated with a corresponding reduction in drinking. These studies have generally been hampered by small sample sizes and a number of confounding variables (e.g., the mixture of patients with major depression and dysthymia, primary alcoholism and primary depression, and patients with and without coexisting panic disorder), all of which render clear interpretation of these data difficult.

Studies of antidepressants in depressed opioid addicts receiving methadone maintenance treatment have been plagued by analogous methodological problems, and have thus yielded similarly modest results. In most such studies, depression was diagnosed on the basis of a current assessment of depressive symptoms rather than a lifetime clinical historical assessment. Moreover, virtually all of these studies have had small sample sizes, thus increasing the possibility of a type II error (i.e., accepting a false-negative result as true) in the interpretation of results. As with the studies of depressed alcoholics, the effect of antidepressants on mood has been more robust than the effect on drug use (Weiss and Mirin 1989). In a recent study of imipramine in 17 methadone maintenance patients with either primary or chronic depression, 9 (53 percent) improved on measures of both mood and drug use after being treated with imipramine for a period of time ranging from 6 weeks to 11 months (Nunes et al. 1991). However, patients with dysthymia and major depression were both included, and the potential confounding effect of coexisting panic disorder in some patients may have affected these results. Moreover, this was an open-label study, and previous work with this population has shown the potential importance of a response to either a placebo or the extra attention and psychosocial treatment given to research subjects (Kleber et al. 1983).

Ziedonis and Kosten (1992, p. 365) conducted a comparative study of amantadine, desipramine, and placebo in 20 depressed and 74 nondepressed cocaine-abusing methadone maintenance patients; all patients also received relapse prevention treatment. The depressed patients who were treated with placebo had a significantly worse treatment outcome than the nondepressed group. However, the depressed patients who were treated with medication reported significantly less cocaine use than the depressed patients who were given placebo. Thus, these data suggest that relapse prevention treatment alone is not

particularly effective for depressed, cocaine-abusing methadone maintenance patients. However, a combination of relapse prevention treatment and medication may be beneficial for this population.

In sum, while there are some encouraging findings regarding the potential efficacy of antidepressants in substance abusers with coexisting depression, methodological difficulties involved in performing these studies have limited the generalizability of their results. Moreover, the most powerful effect of antidepressants in these patients appears (not surprisingly) to be a reduction in depressive symptoms. Unfortunately, while this may be associated with a corresponding reduction in substance use in some patients, this is not universally true. This appears to be an area in which the interaction between psychotherapeutic interventions and pharmacotherapies could be very important and should be studied. For example, it would be important to know which patients exhibit improvement in their mood symptoms and are thus able to reduce or stop their substance use, and which patients are not. It is possible, for instance, that factors that influence the likelihood of improvement in substance use are independent of the nature and/or severity of the patient's coexisting mood disorder. Conversely, it would be important to study patients who do not respond to an antidepressant with mood improvement, but who are able to stop their drug use anyway; such patients may be responding more powerfully to a psychosocial intervention.

BIPOLAR DISORDER

Studies of pharmacologic treatment of patients with substance abuse and bipolar disorder have yielded mixed results. Although an early small study by Gawin and Kleber (1984) found that lithium helped cocaine abusers with cyclothymic or bipolar disorder, a subsequent study by Nunes and colleagues (1990) showed that lithium did not help to reduce cocaine use in patients with cocaine dependence and bipolar spectrum disorder. These studies involved only 5 and 10 patients respectively, and are thus limited by their increased likelihood of generating a type II error. The authors are aware of no research on the effect of integrating psychological and pharmacologic approaches to the treatment of patients with bipolar disorder and substance abuse.

Although Goodwin and Jamison (1990) report that there are no specific guidelines for the treatment of patients with coexisting drug dependence

and bipolar disorder, they postulate that clinical care for these patients should follow the same general guidelines for bipolar patients with alcohol dependence. They specify that bipolar patients with or without alcohol use disorders need to be informed about their increased morbidity risk if they drink alcohol. Specifically, such patients need to be told that (1) alcohol has additive and sometimes synergistic effects with lithium, which may affect judgment and driving; (2) lithium can alter the nature of alcohol intoxication; (3) alcohol can affect an individual's ability to comply with a prescribed medication regimen; (4) alcohol can alter sleep patterns, which can exacerbate or precipitate mania or mixed states; (5) alcohol can induce mood changes in susceptible individuals; and (6) patients with mixed states are especially vulnerable to decreased treatment response if they drink alcohol.

Himmelhoch and colleagues (1983) have written that patients with co-occurring bipolar disorder and alcohol dependence are likely to need more frequent outpatient visits, an increased number of brief hospitalizations, family and group therapy, and other strategies to mobilize a social network. They posit that inpatient treatment programs that are organized to treat both disorders concurrently are also useful for these patients. Although patients with bipolar and substance use disorders sometimes benefit from attending self-help groups such as Alcoholics Anonymous and Narcotics Anonymous, such patients may need to be forewarned that certain self-help group members may not understand their need for prescribed medications such as lithium. Thus, their need for the medication must be particularly emphasized by the physician.

ANXIETY DISORDERS

Several studies (Kleinman et al. 1990; Nunes et al. 1989; Rounsaville et al. 1991) have revealed that a substantial minority of patients with substance use disorders also suffer from coexisting anxiety disorders. Quitkin and colleagues (1972) published an early report on successful imipramine treatment of a small group of patients with coexisting substance abuse and panic disorder; both their drinking behavior and their panic attacks improved. Since then, however, the treatment of patients with these coexisting disorders has received relatively little attention. Two studies of patients with substance use disorders and generalized anxiety disorder revealed that treatment with buspirone improved patients' levels of anxiety. However, drinking behavior was not

significantly improved in the study by Tollefson and colleagues (1992), in which 51 outpatients were randomly assigned to a 24-week trial of either buspirone or placebo; substance use was not measured as an outcome variable in a study of 60 patients with coexisting anxiety and substance abuse, reported by Olivera and colleagues (1990). The interaction between psychosocial treatment and pharmacologic treatment was not discussed in either of these reports.

The use of benzodiazepines in the treatment of patients with coexisting substance use disorders and anxiety disorders has long been the subject of controversy. Although some authors (Annitto and Dackis 1990) argue that the ongoing use of benzodiazepines in this population is contraindicated, others (Adinoff 1992; Ciraulo et al. 1988; Lydiard 1990) have argued that a subgroup of patients who do not respond to other psychosocial or pharmacologic treatments may be treated successfully with benzodiazepines without abusing them. Indeed, Adinoff (1992) recently described a series of seven alcohol-dependent patients who had been prescribed benzodiazepines for several years while maintaining substantial periods of abstinence from alcohol and not developing evidence of benzodiazepine abuse. Adinoff (1992) cautioned that these patients are unusual, and that developing double-blind studies to further delineate the characteristics of benzodiazepine responders may be impractical. However, such reports point out the critical importance of developing specific psychosocial treatment strategies that may help patients in a high-risk group (e.g., patients with substance use disorders) to be able to tolerate treatment with a pharmacologic agent, e.g., a benzodiazepine, that might otherwise not be prescribed.

PSYCHOTIC DISORDERS

Much of the literature on the treatment of dually diagnosed patients has focused on patients with substance use disorders and chronic psychotic illness (Minkoff and Drake 1991; Pepper et al. 1981; Rosenthal et al. 1992a). However, unlike studies of patients with mood disorders, research on this population has focused primarily on psychosocial approaches (Hellerstein and Meehan 1987; Kofoed et al. 1986; Rosenthal et al. 1992b). Indeed, the authors are aware of only one study of this population that specifically investigated the effects of a medication on substance use in a population of patients with schizophrenia. Ziedonis and colleagues (1992) conducted a 12-week, open-label study of 27 outpatients with schizophrenia who were abusing cocaine. Twelve

patients received desipramine plus antipsychotic agents, whereas 15 patients received antipsychotic medications alone. All patients participated in a Dual Diagnosis Relapse Prevention program, which integrates psychiatric social skills training with relapse prevention techniques traditionally used in substance abuse programs. Patients receiving desipramine in this context had a rate of cocaine-positive urine screens that was similar to that of the patients not receiving desipramine during the first 2 months of treatment. However, in the third and final month of the study, patients given desipramine and antipsychotics had significantly fewer cocaine-positive urines than did the patients receiving antipsychotics alone (10 percent versus 56 percent, $p < .001$). Moreover, the researchers pointed out that 70 percent of the patients in this study completed the 12-week treatment program, as compared to a 27 percent completion rate among their patients without coexisting chronic mental illness. Although treatment retention was somewhat greater in the group receiving desipramine (83 percent versus 60 percent), this difference was not statistically significant. These data therefore suggest that the Dual Diagnosis Relapse Prevention program may have been largely responsible for this high completion rate.

Other psychosocial treatment strategies with chronically psychotic substance abusers have also shown some promise. Most of these approaches emphasize the importance of integrating aspects of substance abuse and psychiatric treatment both theoretically (Minkoff 1989) and geographically (Rosenthal et al. 19926). Integrated treatment for these patients may include psychotropic medications, supportive psychotherapy, peer group support of sobriety, psychoeducation, drug abuse counseling, self-help groups, case management, family support, and occupational therapy (Rosenthal et al. 1992b). Drake and colleagues (1993) have emphasized the importance of training mental health professionals regarding substance use issues as a means of providing integrated treatment. It is important to adapt standard mental health and substance abuse treatment approaches to fit the specific needs of dually diagnosed psychotic patients. For example, integrated treatment may differ from traditional substance abuse treatment insofar as it views abstinence as a long-term treatment goal rather than as a short-term treatment requirement, since patients with psychotic illnesses may have more frequent relapses and may be initially difficult to engage (Carey 1989; Rosenthal et al. 19926). Adaptation of treatment techniques for dually diagnosed psychotic patients also includes prescription and monitoring of psychotropic medications that are mindful of the patients' substance dependence (Carey 1989); a realization that while some

patients may benefit from self-help group attendance, the increased frequency of paranoid ideation in this population may make self-help groups counterproductive for some; and decreased use of confrontation in group and individual treatment, because of the difficulty that chronically psychotic patients generally experience with this approach (Kofoed and Keys 1988; Rosenthal 1992b).

Integrated treatment models have been described for both inpatient, outpatient, and day hospital settings. For example, Minkoff (1989) has described an integrated treatment program for hospitalized substance-abusing psychotic patients that utilizes the principles of combined treatment described above. This dual diagnosis inpatient unit is designed to simultaneously stabilize both psychiatric and substance use disorders, engage the patient in both forms of treatment, and provide education and referrals for prolonged stabilization and rehabilitation. However, outcome data from such studies are limited. Ries and Ellingson (1990) have described an integrated model of dual diagnosis treatment in an inpatient setting, but have published pilot (albeit encouraging) data on only 17 patients at 1 -month followup. Kofoed and Keys (1988) reported on a group therapy intervention for dually diagnosed patients admitted to a general psychiatric unit; the group was co-led by a staff member from the substance abuse program and a staff member from the psychiatric unit. The authors compared 109 patients on the unit that had the dual diagnosis group with 109 patients from a similar inpatient unit in the same hospital that had no dual diagnosis group. They found that the unit with the group more frequently developed discharge plans that included substance abuse treatment. However, the patients were not followed up beyond discharge.

Although a number of outpatient programs for this population also have been described, these, too, have presented relatively little outcome data. Drake and colleagues (1993) recently reported 4-year outcome data from an integrated outpatient program for patients diagnosed with both schizophrenia and alcohol dependence. Of 18 patients followed at 4 years, 61 percent had achieved stable remission from alcohol dependence. Alfs and McClellan (1992) designed an 8-week day hospital program for dually diagnosed patients and found that fewer patients completed this program (66 percent) than completed the regular day hospital program (77 percent), although the relapse rate among those in the dual diagnosis program (33 percent) was lower than anticipated. Fariello and Scheidt (1989) reported on a citywide case management program that was implemented in San Francisco for substance abusing chronically

psychotic patients, but outcome results for those patients are not available. Rosenthal and colleagues (1992a, 19926) have implemented a 4-year pilot program of weekly outpatient group treatment for substance-abusing psychotic patients. Patients from a dual diagnosis inpatient unit are randomly assigned either to the dual diagnosis outpatient group at discharge or to traditional separate mental health and substance abuse treatment modalities. Although descriptive data for the 30 enrolled patients have been published (Rosenthal et al. 1992a, 1992b), outcome data are not yet available. However, the authors reported an earlier pilot study of 10 patients with schizophrenia and substance dependence who attended a weekly outpatient dual diagnosis group, and they found a decreased rate of rehospitalization for these patients during the year following enrollment in the group (Hellerstein and Meehan 1987). Kofoed and colleagues (1986) have described a pilot program with 32 patients enrolled in a dual diagnosis outpatient group and have reported that although treatment retention was only 34 percent at 3 months, it remained stable at this rate at 24 months followup.

Despite the promising early reports on the treatment of chronically mentally ill substance abusers, the authors are aware of no published studies that have reported data comparing different models of treatment and their relative efficacy in these patients; specifically, no studies that have compared the effect of two different psychosocial interventions on the effectiveness of a psychopharmacologic treatment approach in this population. Clearly, one reason for this is the lack of research on the effect of medications alone for these patients. The early positive findings from the study of cocaine-abusing schizophrenics by Ziedonis and colleagues (1992) suggest that the investigation of the effect of psychosocial treatment on this process is worthy of further study.

SUMMARY AND RECOMMENDATIONS

Despite the high rate of co-morbidity of substance use disorders and other psychiatric disorders, the research literature on the treatment of these dually diagnosed patients remains relatively sparse. Much of what is written about the treatment of these patients is anecdotal, theoretical, descriptive, or uncontrolled; most empirical studies with these patients have involved small numbers of patients, whose heterogeneity has often made interpretation of data very difficult. Controversies in the field over diagnostic methodology, e.g., how to diagnose coexisting psychiatric

disorders in substance abusers (Weiss et al. 1992b), has only served to further hamper the advance of knowledge in this field.

Among the treatment studies in dually diagnosed patients that have been performed, virtually none have examined the interaction between psychological and pharmacological treatment approaches. The use of medications with these patients has generally focused on treatment of the psychiatric disorder, fueled by the hope that this will improve outcome in the coexisting substance use disorder. For the most part, this hope has been incompletely fulfilled, as most such studies demonstrate more improvement in psychiatric symptomatology than in substance use. Although comprehensive psychosocial approaches to patients with coexisting substance use disorders and psychotic illness have proved promising, these findings can only be regarded as preliminary at this time.

The discrepancy between the improvement in psychiatric symptoms and substance use highlights the potential importance of the development of specific behavioral or psychotherapeutic treatment modalities to treat these dually diagnosed patients.

It is known, for example, that the treatment of carefully diagnosed anxiety, mood, and psychotic disorders with appropriate medications helps those disorders. It also is becoming clearer that the pharmacologic treatment of patients with these disorders plus a substance use disorder in the absence of a specific psychosocial treatment program designed for this population is not optimally effective in treating the coexisting substance use disorder. Rather, some combination treatment, similar to the promising data of Ziedonis and colleagues (1992), who integrated Dual Diagnosis Relapse Prevention treatment with desipramine for cocaine-abusing schizophrenic patients, is needed in the treatment of other dually diagnosed patients. In developing such psychological therapies, it is important to recognize the heterogeneity of dually diagnosed patients (Weiss et al. 1992a), and to not necessarily assume that a dual diagnosis psychosocial treatment that is successful for chronically psychotic patients also will be useful for patients with panic disorder, dysthymia, personality disorders, or other psychiatric illnesses. Rather, research is needed in the development of specific psychosocial treatment techniques for specific subgroups of dually diagnosed patients in order to enhance the known benefits of pharmacotherapy and improve overall treatment outcome in this population.

REFERENCES

Adinoff, B. Long-term therapy with benzodiazepines despite alcohol dependence disorder. *Am J Addict* 1(4):288-293, 1992.

Alfs, D.S., and McClellan, T.A. A day hospital program for dual diagnosis patients in a VA medical center. *Hosp Community Psychiatry* 43:241-244, 1992.

Annitto, W.J., and Dackis, CA. Use of benzodiazepines by alcoholics. Reply. *Am J Psychiatry* 147: 129, 1990.

Beitman, B.D., and Klerman, G.L. *Integrating Pharmacotherapy and Psychotherapy*. Washington, DC: American Psychiatric Press, Inc., 1991.

Carey, K.B. Emerging treatment guidelines for mentally ill chemical abusers. *Hosp Community Psychiatry* 40:341-343, 1989.

Caton, C.L.M.; Gralnick, A.; Bender, S.; and Simon, R. Young chronic patients and substance abuse. *Hosp Community Psychiatry* 40:1037-1040, 1989.

Ciraulo, D.A., and Jaffe, J.H. Tricyclic antidepressants in the treatment of depression associated with alcoholism. *J Clin Psychopharmacol* 1:146-150, 1981.

Ciraulo, D.A.; Sands, B.F.; and Shader, R.I. Critical review of liability for benzodiazepine abuse among alcoholics. *Am J Psychiatry* 145:1501-1506, 1988.

Drake, R.E.; McHugo, G.J.; and Noordsy, D.L. Treatment of alcoholism among schizophrenic outpatients: 4-year outcomes. *Am J Psychiatry* 150:328-329, 1993.

Drake, R.E.; Osher, F.C.; and Wallach, M.A. Alcohol use and abuse in schizophrenia: A prospective community study. *J New Ment Dis* 177:408-414, 1989.

Drake, R.E., and Wallach, M.A. Substance abuse among the chronic mentally ill. *Hosp Community Psychiatry* 40:1041-1046, 1989.

Fariello, D., and Scheidt, S. Clinical case management of the dually diagnosed patient. *Hosp Community Psychiatry* 40:1065-1067, 1989.

Gawin, F.H., and Kleber, H.D. Cocaine abuse treatment: Open pilot trial with desipramine and lithium carbonate. *Arch Gen Psychiatry* 41:903-909, 1984.

Goodwin, F.K., and Jamison, K.R. *Manic Depressive Illness.* New York: Oxford University Press, 1990.

Hellerstein, D.H., and Meehan, B. Outpatient group therapy for schizophrenic substance abusers. *Am J Psychiatry* 144:1337-1339, 1987.

Himmelhoch, J.M.; Hill, J.S.; and Steinberg, B. Lithium, alcohol, and psychiatric diagnosis. *J Psychiatr Treat Eval* 5:83-88, 1983.

Karasu, T.B. Psychotherapy and pharmacotherapy: Toward an integrative model. *Am J Psychiatry* 139:1102-1114, 1982.

Kleber, H.D.; Weissman, M.M.; Rounsaville, B.J.; Wilber, C.H.; Prusoff, B.A.; and Riordan, C.E. Imipramine as treatment for depression in addicts. *Arch Gen Psychiatry* 40:649-653, 1983.

Kleinman, P.H.; Miller, A.B.; Millman, R.B.; Woody, G.E.; Todd, T.; Kemp, J.; and Lipton, D.S. Psychopathology among cocaine abusers entering treatment. *J New Ment Dis* 178:442-447, 1990.

Klerman, G.L. Ideological conflicts in integrating pharmacotherapy and psychotherapy. In: Beitman, B.D., and Klerman, G.L., eds. *Integrating Pharmacotherapy and Psychotherapy.* Washington, DC: American Psychiatric Press, Inc., 1991.

Kofoed, L.; Kania, J.; Walsh, T.; and Atkinson, R.M. Outpatient treatment of patients with substance abuse and coexisting psychiatric disorders. *Am J Psychiatry* 143:867-872, 1986.

Kofoed, L., and Keys, A. Using group therapy to persuade dual-diagnosis patients to seek substance abuse treatment. *Hosp Community Psychiatry* 39:1209-1211, 1988.

Kosten, T.R.; Rounsaville, B.J.; and Kleber, H.D. Multidimensionality and prediction of treatment outcome in opioid addicts: 2.5-year follow-up. *Compr Psychiatry* 28:3-13, 1987.

Lydiard, R.B. Use of benzodiazepines by alcoholics. Letter to the editor. *Am J Psychiatry* 147:128-129, 1990.

Mason, B.J.; Kocsis, M.D.; and Ritvo, E.C. "Desipramine for Secondary Depression in Alcoholism." Presented at the 145th Annual Meeting of the American Psychiatric Association, Washington, DC, May 2-7, 1992.

McLellan, A.T. "Psychiatric severity" as a predictor of outcome from substance abuse treatments. In: Meyer, R.E., ed. *Psychopathology and Addictive Disorders.* New York: Guilford Press, 1986.

McLellan, A.T., and Druley, H.A. Non-random relation between drugs of abuse and psychiatric diagnosis. *J Psychiatr Res* 13:179-184, 1977.

McLellan, A.T.; Luborsky, L.; Woody, G.E.; and O'Brien, C.P. Are the "addiction-related" problems of substance abusers really related? *J New Ment Dis* 169:68-74, 1981.

McLellan, A.T.; Luborsky L.; Woody, G.E.; O'Brien, C.P.; and Druley, K.A. Predicting response to drug and alcohol treatments: Role of psychiatric severity. *Arch Gen Psychiatry* 40:620-625, 1983.

McLellan, A.T.; O'Brien, C.P.; Metzger, D.; Alterman, A.I.; Comish, J.; and Urschel, H. Is substance abuse treatment effective-compared to what? In: O'Brien, C.P., and Jaffe, J., eds. *Addictive States.* New York: Raven Press, 1992.

Meyer, R.E. How to understand the relationship between psychopathology and addictive disorders: Another example of the chicken and the egg. In: Meyer, R.E., ed. *Psychopathology and Addictive Disorders.* New York: Guilford Press, 1986b.

Meyer, R.E. *Psychopathology and Addictive Disorders.* New York: Guilford Press, 1986a.

Minkoff, K. An integrated treatment model for dual diagnosis of psychosis and addiction. *Hosp Community Psychiatry* 40:1031-1036, 1989.

Minkoff, K., and Drake, R.E. *Dual Diagnosis of Major Mental Illness and Substance Disorder.* San Francisco: Jossey-Bass, Inc., 1991.

Mirin, S.M. *Substance Abuse and Psychopathology.* Washington, DC: American Psychiatric Press, Inc., 1984.

Mirin, S.M.; Weiss, R.D.; Griffin, M.L.; and Michael, J.L. Psychopathology in drug abusers and their families. *Compr Psychiatry* 32:36-51, 1991.

Nunes, E.V.; McGrath, P.J.; Quitkin, F.M.; Stewart, J.P.; Harrison, W.; Tricamo, E.; and Ocepek-Welikson, K. Imipramine treatment of alcoholism with comorbid depression. *Am J Psychiatry* 150:963-965, 1993.

Nunes, E.V.; McGrath, P.J.; Wager, S.; and Quitkin, F.M. Lithium treatment for cocaine abusers with bipolar spectrum disorders. *Am J Psychiatry* 147:655-657, 1990.

Nunes, E.V.; Quitkin, F.M.; Brady, R.; and Stewart, J.W. Imipramine treatment of methadone maintenance patients with affective disorder and illicit drug use. *Am J Psychiatry* 148:667-669, 1991.

Nunes, E.; Quitkin, F.; and Klein, D. Psychiatric diagnosis in cocaine abuse. *Psychiatry Res* 28:105-114, 1989.

Olivera, A.A.; Sarvis, S.; and Heard, C. Anxiety disorders coexisting with substance dependence: Treatment with buspirone. *Curr Ther Res* 47:52-61, 1990.

Pepper, B.; Kirshner, M.C.; and Ryglewicz, H. The young adult chronic patient: Overview of a population. *Hosp Community Psychiatry* 32:463-469, 1981.

Quitkin, F.M.; Rifkin, A.; Kaplan, J.; and Klein, D.F. Phobic anxiety syndrome complicated by drug dependence and addiction. *Arch Gen Psychiatry* 27:159-162, 1972.

Regier, D.A.; Farmer, M.E.; Rae, D.S.; Locke, B.Z.; Keith, S.J.; Judd, L.L.; and Goodwin, F.K. Comorbidity of mental disorders with alcohol and other drug abuse: Results from the Epidemiological Catchment Area (ECA) study. *JAMA* 264:2511-2518, 1990.

Ridgely, M.S. Creating integrated programs for severely mentally ill persons with substance disorders. In: Minkoff, K., and Drake, R.E., eds. *Dual Diagnosis of Major Mental Illness and Substance Disorder.* San Francisco: Jossey-Bass, Inc., 1991.

Ries, R.K., and Ellingson, T. A pilot assessment at one month of 17 dual diagnosis patients. *Hosp Community Psychiatry* 41:1230-1233, 1990.

Rosenthal, R.N.; Hellerstein, D.J.; and Miner, C.R. Integrated services for treatment of schizophrenic substance abusers: Demographics, symptoms, and substance abuse patterns. *Psychiatr Q* 63:3-26, 1992a.

Rosenthal, R.N.; Hellerstein, D.J.; and Miner, C.R. A model of integrated services for outpatient treatment of patients with comorbid schizophrenia and addictive disorders. *Am J Addict* 1(4):339-348, 1992b.

Ross, H.E.; Glaser, F.B.; and Germanson, T. The prevalence of psychiatric disorders in patients with alcohol and other drug problems. *Arch Gen Psychiatry* 45:1023-1032, 1988.

Rounsaville, B.J.; Foley Anton, S.; Carroll, K.; Budde, D.; Prusoff, B.A.; and Gawin, F. Psychiatric diagnoses of treatment-seeking cocaine abusers. *Arch Gen Psychiatry* 48:43-51, 1991.

Sarwer-Foner, G.J. An overview of combined psychopharmacology and psychotherapy. In: Greenhill, M.H., and Gralnick, A., eds. *Psychopharmacology and Psychotherapy*. New York: Free Press, 1983.

Siris, S.G. Pharmacological treatment of substance-abusing schizophrenic patients. *Schizophr Bull* 16:111-122, 1990.

Tollefson, G.D.; Montague-Clouse, J.; and Tollefson, S.L. Treatment of comorbid generalized anxiety in a recently detoxified alcoholic population. *J Clin Pharmacol* 12:19-26, 1992.

Weiss, R.D., and Mirin, S.M. Tricyclic antidepressants in the treatment of alcoholism and drug abuse. *J Clin Psychiatry* 50(Suppl 7):4-9, 1989.

Weiss, R.D.; Mirin, S.M.; and Frances, R.J. The myth of the typical dual diagnosis patient. *Hosp Community Psychiatry* 43:107-108, 1992a.

Weiss, R.D.; Mirin, S.M.; and Griffin, M.L. Methodological considerations in the diagnosis of coexisting psychiatric disorders in substance abusers. *Br J Addict* 87: 179-187, 1992b.

Weissman, M.M.; Pottenger, M.; Kleber, H.; Ruben, H.L.; Williams, D.; and Thompson, W.D. Symptom patterns in primary and secondary depression: A comparison of primary depressives with depressed opiate addicts, alcoholics, and schizophrenics. *Arch Gen Psychiatry* 34:854-862, 1977.

Ziedonis, D., and Kosten, T. Depression as a treatment matching factor in cocaine dependence treatment. In: Harris, L., ed. *Problems of Drug Dependence 1991: Proceeding of the 53rd Annual Scientific Meeting.* National Institute on Drug Abuse Research Monograph No. 119. DHHS Pub. No. (ADM)92-1888. Washington, DC: Supt. of Docs., U.S. Govt. Print. Off., 1992.

Ziedonis, D.; Richardson, T.; Lee, E.; Petrakis, I.; and Kosten, T. Adjunctive desipramine in the treatment of cocaine abusing schizophrenics. *Psychopharmacol Bull* 28(3):309-314, 1992.

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Combining Pharmacotherapy With Psychotherapy for Substance Abusers With Borderline Personality Disorder: Strategies for Enhancing Compliance

Marsha M. Linehan

INTRODUCTION

Treatment programs integrating both psychosocial and pharrnacotherapy interventions are commonly recommended across the entire spectrum of mental disorders. As this volume indicates, such integrated treatments increasingly are recommended for the treatment of some substance abuse problems. Combined treatments also may be recommended when the client has a dual diagnosis of substance abuse concurrent with another disorder. In these cases the psychotropic medications often are prescribed for the disorder co-occurring with the substance abuse. The effectiveness of these combined treatment programs depends on the treated individual's ability and willingness to comply with the requirements of both treatment components. In psychosocial interventions, this includes attending treatment sessions and, in the case of cognitive and behavioral therapies, performing requisite homework assignments. In pharmacotherapy, the individual has to take the required medications in the correct doses and, in some cases, refrain from taking other medications or other substances that would counteract or reduce the effectiveness of the prescribed medication.

Compliance with treatment regimes is a continuing cause of concern when treating substance abuse. Noncompliance with psychosocial interventions, particularly premature treatment dropout, is common (Allison and Hubbard 1985). Furthermore, in general psychiatric populations, substance abuse is one of the best predictors of noncompliance with therapy appointments (Matas et al. 1992; Sparr et al. 1993). Medication compliance, in particular, poses several problems. Effective treatment of drug abusers with pharmacotherapy may require a

behavioral capability (i.e., managing drug use responsibly) that the drug abuser simply does not have. Depending on the individual's particular drug use history, prescribed drugs may increase the danger of relapse to the primary drug abuse. Finally, drug abusers in pharmacotherapy also may participate in other treatment programs where use of any medication is proscribed or strongly disapproved of.

While substance abusers are among the most noncompliant Axis I clients, the addition of an Axis II disorder can further exacerbate the problems. Matas and colleagues (1992) found that, in addition to substance abusers, those diagnosed with a personality disorder were less likely than others to follow through on a referral to an outpatient psychiatry program. Among individuals diagnosed with borderline personality disorder (BPD), dropout rates from psychotherapy in most studies average around 50 percent at the 6-month point (Koenigsberg et al., in press). In studies investigating pharmacotherapy in this population, dropout rates also are very high (Cowdry and Gardner 1988). Waldinger and Frank (1989) reported interviews with 36 psychiatrists who prescribed medications for borderline clients. By their report, on average 47 percent of those who received medications in each therapist's practice abused the medication at some point. Eighty-seven percent of the therapists cited medication misuse, including taking other than prescribed dosages or taking an overdose, as a common problem. In a pilot study conducted in this author's research clinic, six of nine (67 percent) suicidal women meeting criteria for BPD abused prescribed medications.

As reviewed elsewhere (Linehan 1993c) the overlap between substance abuse and BPD is substantial. Among individuals meeting criteria for substance abuse, a concomitant diagnosis of BPD is common, ranging from 13 percent in a study of consecutive admissions to an alcohol treatment program (Nace et al. 1983) to 66 percent among psychiatric outpatients (Vaglum and Vaglum 1985). Up to one-third of all substance abusers may show a high number of BPD traits (Tousignant and Kovess 1989). Looking at the overlap from the other direction, individuals meeting criteria for BPD commonly report a history of substance abuse (Akiskal et al. 1985) and score high on substance abuse scales (McCann et al. 1992; Pitts et al. 1985). Estimates suggest that from 57 percent to 84 percent of BPD individuals currently or previously have met criteria for substance abuse or dependence (Dulit et al. 1990; Zanarini et al. 1989), although the estimated number with a primary Axis I diagnosis of substance abuse is much lower at 21 percent (Koenigsberg et al. 1985). BPD substance abusers are uniformly more disturbed than those abusers

who do not meet criteria for BPD. They are more commonly co-morbid for depressive disorders, have more frequent suicide attempts and accidents, and score higher on impulse dyscontrol and antisocial tendencies and lower on reality testing (Inman et al. 1985; Kosten et al. 1989).

Borderline clients, like substance abusers, are notoriously difficult to treat. Although their frequent suicidal threats and parasuicidal behaviors coupled with frequent displays of hostility and anger are important causes of this difficulty, problems in obtaining compliance with therapy regimes also are a frequent source of conflict in the treatment of these individuals. Over the last several years, Linehan and colleagues (1991; in press-u) have developed and evaluated an outpatient psychosocial behavioral intervention for chronically impaired individuals meeting criteria for BPD. The treatment, Dialectical Behavior Therapy (DBT), is multimodal, flexible, and manualized (Linehan 1993a, 19936; Linehan et al., in press-b). Aspects of the treatment were designed specifically to address the multiple compliance problems encountered in treating BPD. It is these specific treatment strategies that will be discussed in this chapter. The general application of DBT to substance abuse problems has previously been outlined and, thus, will only be summarized briefly here.

DBT OVERVIEW

DBT is based on a biosocial model that synthesizes motivational and capability deficit models of behavioral dysfunction (including substance abuse and borderline behavioral patterns) theorizing that (1) individuals with behavioral dysfunctions lack important interpersonal, self-regulation (including emotion regulation), and distress tolerance skills, and (2) personal and environmental factors both inhibit the use of behavioral coping skills the individual does have and often reinforce dysfunctional behavioral patterns. The tension between these two models, capability deficit versus faulty motivation, is reflected in the frequent conflict between etiological formulations that focus on commitment and client responsibility as crucial to change (motivational models) and those that focus on acceptance (surrender in Alcoholics Anonymous [AA] terms) and development of new capabilities (relapse prevention models) as crucial to change. In DBT, treatment requires commitment and client responsibility, on the one hand, and, on the other, focuses considerable therapeutic energy on accepting and validating the patient's current

condition. Therapeutic contingencies that reinforce functional behaviors and extinguish or punish dysfunctional behaviors are balanced by efforts aimed at increasing the client's capacity to emit the requisite functional behaviors. Confrontation is balanced by support. It was the tension and ultimate resolution of this essential conflict between demanding that the client change this very moment versus acceptance of the client as is that led to the use of dialectics in the title of the treatment. As a world view, furthermore, dialectics anchor the treatment within other perspectives that emphasize (1) the holistic, systemic, and interrelated nature of human functioning and reality as a whole, asking always "what is being left out of our understanding here"; (2) searching for synthesis and balance to replace the rigid, often extreme, and dichotomous responses characteristic of severely dysfunctional individuals; and (3) enhancing comfort with ambiguity and change, which are viewed as inevitable aspects of life.

With severely dysfunctional clients, including serious substance abusers, DBT assumes that, on the one hand, necessary skill training is extraordinarily difficult (if not impossible) within the context of a therapy oriented to reducing motivation to engage in dysfunctional behaviors (including drug abuse), and, on the other hand, sufficient attention to motivational issues cannot be given in a treatment with the rigorous control of therapy agenda needed for skill training. To resolve this dilemma, the treatment is divided into two components: one that focuses primarily on skill acquisition and one that focuses primarily on motivational issues and skill strengthening. A third component is added to foster generalization of skills to the individual's everyday life. In outpatient DBT, these modes are psychosocial groups (for skills training), individual psychotherapy (addressing motivational issues and skills strengthening), and telephone contact with the individual therapist (addressing generalization). This mixture of many different modes of treatment for the individual is similar to the highly complex treatment programs often used with substance abusers (Hubbard 1992, pp. 596-611).

In DBT as a whole, the hierarchy of treatment targets, from most to least important, is very specific and clear as follows: (1) reducing suicidal and other life-threatening behaviors; (2) reducing therapy-interfering behaviors (including noncompliance); (3) reducing severe quality-of-life interfering behaviors (including serious substance abuse); (4) increasing skillful coping behaviors, including distress tolerance, emotion regulation, interpersonal effectiveness, and mindfulness; (5) reducing posttraumatic stress responses; (6) enhancing self-respect; and (7) other

goals of the client. The hierarchy for individual psychotherapy is the same as for the treatment as a whole, and the agenda of each individual psychotherapy session is set weekly depending on the client's behavior since the last session. Target behaviors are focused on according to the hierarchy and recursively as higher priority behaviors reappear. High-priority behaviors are never ignored in DBT. Information about the client's behaviors since the last session can come from a number of sources, including direct contact with the client, collateral reports or phone calls, urinalyses or blood tests, verbal report by the client at the beginning of the session, and weekly diary cards that the client brings to each session. Besides information about suicidal ideation and deliberate self-injurious behaviors during the week, the diary cards also elicit information about daily use of prescribed, over-the-counter, and illicit drugs. Failure to complete or bring the cards to the session and, if necessary, dishonesty are targeted directly as therapy-interfering behaviors.

PROTOCOL FOR COMBINING PHARMACOTHERAPY WITH DBT

There is nothing in DBT that proscribes ancillary mental health care not offered in DBT as long as these programs of treatment are clearly ancillary to DBT and are not the primary treatment. Outpatients may be admitted for brief psychiatric inpatient visits or residential substance abuse programs; take psychotropic medications and see a physician, nurse, or other pharmacotherapist for monitoring; participate in behavioral skills classes offered in the community; attend group meetings and meet with their counselor in residential treatment communities; see a case manager associated with ancillary treatment; go to marriage counseling, vocational counseling, or movement therapy; participate in day treatment; and attend AA, Narcotics Anonymous, or similar meetings. Clients also are likely to make occasional contact with other mental health care professionals in crisis clinics and emergency rooms, for example.

There are specific case management strategies that guide DBT therapists in their interactions with ancillary treatment programs, including with pharmacotherapists. The spirit of these strategies is that the primary role of the DBT therapist is as consultant to the client rather than to the client's network. The overriding implication of this is that, in general, DBT therapists do not intervene to adjust environments for the sake of

the client, nor do they consult with other ancillary professionals about how to treat the client unless the client is present. The client, not the therapist, is the intermediary between the treatment program and other professionals, including pharmacotherapists. The therapist's job is to consult with the client on how to interact effectively with the environment, rather than consult with the environment on how to interact effectively with the client.

The consultation-to-the-client strategies are guided by three objectives. First, the aim of treatment is to teach clients how to manage their own lives and care for themselves. The consultant strategy both assumes and targets enhancement of clients' abilities to take care of themselves, to interact effectively with medical professionals, and to obtain whatever services they may need. Second, the consultant strategy was designed to decrease instances of "splitting" between DBT therapists and other professionals treating the client. Splitting occurs when different professionals in the person's network hold differing opinions on how to treat the client. By remaining in the role of a consultant to the client, the therapist stays out of such arguments. Third, the consultant strategy promotes respect for clients by imparting the message that they are credible, believable, reliable, and capable of performing interventions on their own behalf. Because health care professionals routinely exchange information, routine use of the consultant strategy ordinarily requires orienting ancillary professionals to the strategy. Although consultation between professionals actually is encouraged, not discouraged, the requirement that clients be present (and, preferably, arrange the consultation) is somewhat different than usual consultation in the community. In consulting with an ancillary pharmacotherapist, therefore, the DBT therapist attends joint meetings with the client or arranges to speak via speakerphone to the pharmacotherapist while the client is actually present. For every rule, of course, there are exceptions and, in medical emergencies or when the immediate safety of the client is an issue, the DBT therapist does whatever is necessary to protect the client. But, similar to the rehabilitation medicine model, in DBT the capabilities of the client rather than the disabilities are the most immediate focus of attention.

In standard DBT, the primary therapist (usually the psychotherapist) does not supervise, manage, or prescribe psychotropic medications. Instead, the role of the psychotherapist is to consult with the client about how to interact effectively with physicians and nurse practitioners who do prescribe and manage psychotropic medications. The goal is to teach the

client to be a responsible and competent medical consumer. This policy of separating psychosocial from pharmacotherapy interventions came directly from the findings cited above that BPD clients often abuse prescribed medications. In this author's pilot work, it became increasingly clear that when the primary therapist had the role of drug prescriber, the client had an incentive to lie about drug abuse as a means of obtaining more drugs from the therapist. From a behavioral point of view, this rendered the therapist almost totally ineffective in the role of teacher of proper drug use. Essentially, the therapist was in the position of power with the ability to dispense the potent reinforcers that drugs constitute, and such a role interfered with the ability of the therapist to work collaboratively with the client regarding the proper use of medications.

Misuse or abuse of prescribed drugs, according to the target hierarchy described above, would be addressed in DBT as a first priority when it is immediately life threatening or done as a way of intentionally harming the self (e.g., parasuicidal behavior, including suicide attempts). Misuse or abuse of prescribed drugs would be targeted as a second priority (i.e., as therapy-interfering behavior) when the drugs misused were prescribed as part of DBT or as ancillary treatment for either substance abuse or other mental health problems. All other substance abuse would be targeted as a third priority, at least when it is clear that a life of quality is not possible unless the substance abuse is stopped. Drug misuse is treated using the same strategies as in treating any other problematic targeted behavior. Briefly, these strategies require the therapist to balance validation strategies with problem-solving strategies. Problem solving in DBT consists of behavioral analyses of the dysfunctional behavior, analyses of alternative functional responses, implementation of necessary procedures to develop the requisite behavioral capabilities (skills training) or improve motivation (application of contingency management, exposure techniques, and cognitive modification), and application of commitment strategies designed to enhance compliance and change.

COMPLIANCE-ENHANCING DBT STRATEGIES

A number of treatment strategies and protocols were developed specifically to enhance both the capability and the motivation of clients to comply with the DBT treatment regime. Although data suggest that DBT is quite successful at enhancing treatment retention (Linehan et al. 1991), it is not clear which components of the treatment actually are conducive

to high compliance rates. What follows is a description of DBT strategies that either were designed specifically to enhance compliance or are likely related to compliance on theoretical grounds. While these strategies are a small part of the treatment overall, they may nonetheless be important in this context.

Orienting and Commitment Strategies

Clearly specified orienting and commitment strategies are used during the first several meetings with clients to orient them to what DBT is about, what is expected of them, what they can expect of the therapist, and, in general, how and why the treatment is expected to work. The orientation, or pretreatment meetings, are held at the very beginning between the client and the intake person, and the goal is to forge a commitment between the individual and the treatment program as a whole to work together as a therapy team. Separate meetings then are held with the individual therapist and with the group leaders to organize mutual commitments between the individual therapist and client and between the group leaders and the client. The first meeting of the group therapy itself is a repeat of this process, and the goal is to obtain the commitment of the group as a whole (including the group leaders) to work together. Thereafter, the orienting and commitment strategies are used for reorientation and recommitment whenever the client (1) is violating the therapy contract or is threatening to (e.g., says he or she is quitting the skills training); (2) is threatening suicide or other dysfunctional behaviors, such as substance abuse; (3) appears to be making unrealistic demands or have unrealistic expectations of the therapists or therapy; or (4) is having difficulty using therapy appropriately (e.g., doesn't call the therapist when appropriate because of fear of imposing). In short, the treatment contract is made over and over again.

Orienting. Orienting involves giving clients task information about the process and requirements of treatment as a whole, about a specific treatment procedure, and about what is required to implement a specific course of action decided upon during problem solving. The rationale here is that many apparent treatment failures to learn or change stem from failures to understand what must be learned or changed or from misunderstandings of the conceptual model underlying the treatment procedure being used. Role induction has been shown to enhance treatment retention in psychotherapy in general (LaTorre 1977) and may enhance retention in substance abuse programs. In DBT, role induction is used to clarify expectations about treatment, to enhance positive outcome

expectancies, and to communicate and agree on the time limits of the treatment. Problems that may arise in establishing and maintaining a therapeutic alliance are discussed, and problem-solving is begun right from the start. In addition, very similar procedures are used at every point in therapy where some positive behavioral change or effort is expected, for example when giving behavioral homework assignments or when resolving conflicts about treatment or personal limits of the therapist.

Clarity of Dropout Rules. In DBT, the initial treatment contract is for a specified period of time, usually either 6 months or 1 year. Renewal of the contract is contingent on the client improving during the initial period of treatment. For clients who wish to maintain the therapeutic relationship, this contingency counteracts their fear that improvement will result in loss of therapy. In addition, rules for number of allowed missed sessions are clearly specified. In standard DBT, clients are out of the program if they miss 4 scheduled weeks of therapy in a row-either individual or group treatment. If they "drop out" in this manner, they cannot be readmitted to the program until the end of the contracted period. The rule is rigidly enforced and does not depend on whether the reason for missing is deemed "good" or "bad." The premise is that there is never a good reason for missing so many weeks of therapy. The 4-week rule, however, does allow a client to attend a 30-day inpatient substance abuse program without being dropped. In general, however, clients are told that no matter what happens, including inpatient hospitalization, it is their responsibility to get to enough sessions to stay in the program. The clarity and nonnegotiability of this rule is likely effective for several reasons. First, it makes drifting out of therapy more difficult. Many clients miss therapy thinking "I'll go next week." They keep putting off returning until they are actually out. In this system, it is clear how many weeks they can put off coming. Other clients drop out of therapy due to shame or fear about returning after missing only one or two sessions. This system makes it perfectly clear that if three sessions are missed, returning is acceptable.

Commitment Strategies. Commitment to therapy and the therapeutic goals is essential in any psychosocial intervention. With borderline and substance abuse clients, obtaining and keeping behavioral commitments can be especially difficult. DBT relies on a series of strategies that are applied during the first meetings with the client and are reapplied at every point thereafter whenever commitment appears to be slipping. They also are applied whenever new procedures requiring the client's cooperation

are to be implemented and to develop commitment to whatever behavioral solutions the client and therapist arrive at in problem solving. The main commitment strategies in DBT are as follows.

Marketing the treatment program to the community, especially the community of clients, is a critical part of DBT. Marketing is based on the idea that people keep commitments they believe in better than those they do not believe in. Thus, once one or more action plans have been proposed, the therapist engages the client in a discussion of the pros and cons of actually making the proposed commitment to a specific plan or solution. The aim is twofold: (1) to rehearse the good points of the treatment, procedure, or action plan already evaluated and chosen, and (2) to develop counterarguments to reservations that will almost certainly come up later, usually when the client is alone and without help in combating doubts.

Once a tentative commitment is made, the therapist tries to increase the commitment if at all possible by playing the devil's advocate. The idea here is for the therapist to pose arguments against making a commitment. That is, the therapist takes the place of the devil, making sure that the counterarguments to commitment are slightly weaker than the client's arguments for commitment. This tactic also is helpful in enhancing the client's sense of choice and "illusion" of control.

The foot-in-the-door (Freedman and Fraser 1966) and the door-in-the face techniques (Ciadini 1975) are well-known social psychology procedures for enhancing compliance with requests and previously made commitments. (The terms come from the initial research on door-to-door canvassing for donations to charities.) The foot-in-the-door technique increases compliance by making an easier first request followed by a more difficult request (for example, first getting an agreement to set reducing substance abuse as a goal, then asking for a commitment to stay off drugs this week). In the door-in-the-face technique, the procedure is reversed. One first requests something much larger than is actually wanted and then requests something easier (for example, requesting the client first to agree not to use any illicit drugs during the upcoming week, then a request to call the therapist or sponsor before using drugs). A combined procedure, asking first for something very hard, then moving to something very easy, progressing to a more difficult request may at times be the most effective strategy (Goldman 1986). For example, during the initial orientation the therapist may present treatment goals vaguely and favorably, omitting discussing the difficulty of reaching the

goals. After a commitment to these general goals is obtained, the therapist then ups the ante, presenting more fully the difficulties of achieving the goals, and subsequent commitments are obtained. After escalating the difficulties for a few exchanges (each time getting a commitment) the therapist may jump to a very difficult commitment, then reduce somewhat the scope or difficulty of the request and obtain a final commitment.

A variation on the foot-in-the-door tactic is to remind the client of previous commitments. This always is done when the strength of a commitment seems to be fading or when the client's behavior is incongruent with previous commitments. It can be particularly useful in a crisis situation, especially when the client is threatening suicide or some other destructive response. In reminding the client of previous commitments, the therapist also discusses whether the client still has a commitment made previously. If the commitment or goal is essential to DBT (such as committing to working on reducing suicidal behavior) or to the therapist's own limits for conducting therapy, the therapist next moves to establishing a recommitment. If changes do not conflict with DBT or the therapist's limits, then renegotiation of commitments is done. A number of other commitment strategies also are employed such as highlighting the freedom to choose goals and behaviors and the simultaneous absence of reasonable alternatives, using principles of shaping to gradually increase the level of commitment to change, and generating hope via encouragement and appropriate praise.

Focus on Therapy-Interfering Behaviors

As noted above, reducing therapy-interfering behaviors of both client and therapist is the second target in DBT. The focus here is on keeping clients and therapists working together collaboratively. Although this is likely an implicit second priority in most psychotherapies, it is rarely discussed as explicitly as in DBT. However, the chronic nature of most borderline clients' problems, their high tendency to end therapy prematurely, and the likelihood of therapist burnout and iatrogenic behaviors when treating BPD require explicit attention with this population. Both client and therapist behaviors that threaten the relationship or therapeutic progress are addressed in a direct manner immediately, consistently, and constantly, and, most importantly, before either the therapist or the client no longer wants to continue. Interfering behaviors of the client, such as those that interfere with actually receiving the therapy or with other clients benefiting from therapy (in group or

milieu settings) and that bum out or cross the personal limits of the therapist, are treated within therapy sessions. Those of the therapist, including any that are iatrogenic as well as behaviors that unnecessarily cause the client distress or make progress difficult, are dealt with within therapy sessions if brought up by the client but also are dealt with within the consultation/supervision meeting.

SUMMARY

DBT is a comprehensive, behaviorally oriented treatment designed for highly dysfunctional individuals meeting criteria for BPD. Many of these criteria are characteristic of drug abusers, and some of the problems encountered in treatment of drug abusers, especially when various treatments are combined, are similar. The basic armamentarium of the DBT therapist is the balancing of validation and acceptance treatment strategies with problem-solving procedures, including contingency management, exposure-based procedures, cognitive modification, and skills training. In addition, a number of specific strategies have been woven together to enhance compliance and to reduce the staff splitting that is so frequent with this population. Those described in this chapter include orienting and commitment strategies and the focus in DBT on reducing therapy-interfering behavior and on consultation with the client rather than with the client's network.

REFERENCES

Akiskal, H.S.; Chen, SE.; Davis, G.C.; Pusantian, V.R.; Kashgariam, M.; and Bolinger, J.M. Borderline. An adjective in search of a noun. *J Clin Psychiatry* 46:1-48, 1985.

Allison, M., and Hubbard, R.L. Drug abuse treatment process: A review of the literature. *Int J Addict Behav* 20:1321-1345, 1985.

Ciadini, R.B. Reciprocal concessions procedure for inducing compliance: The door-in-the-face technique. *J Pers Soc Psychol* 31:206-215, 1975.

Cowdry, R.W., and Gardner, D.L. Pharmacotherapy of borderline personality disorder: Alprazolam, carbamazepine, trifluoperazine, and tranylcypromine. *Arch Gen Psychiatry* 45:111-119, 1988.

Dulit, R.A.; Fyer, M.R.; Haas, G.L.; Sullivan, T.; and Frances, A.J. Substance use in borderline personality disorder. *Am J Psychiatry* 147:1002-1007. 1990.

Freedman, J.L., and Fraser, S.C. Compliance without pressure: The foot-in-the-door technique. *J Pers Soc Psychol* 4:195-202, 1966.

Goldman, M. Compliance employing a combined foot-in-the-door and door-in-the-face procedure. *J Soc Psychol* 126: 111-116, 1986.

Hubbard, R.L. Evaluation and treatment outcome. In: *Substance Abuse: A Comprehensive Textbook.* Lownson, J.H.; Ruiz, P.; Millman, R.B.; and Langrod, J.G., eds. Baltimore: Williams and Wilkins, 1992.

Inman, D.J.; Bascue, L.O.; and Skoloda, T. Identification of borderline personality disorders among substance abuse inpatients. *J Subst Abuse Treat* 2:229-232, 1985.

Koenigsberg, H.W.; Clarkin, J.; Kernberg, O.F.; Yeomans, F.; and Gutfreund, J. Some measures of process and outcome in the psychodynamic psychotherapy of borderline patients. The integration of research and psychoanalytic practice. In: *Proceedings of the IPA's First International Conference on Research,* in press.

Koenigsberg, H.; Kaplan, R.; Gilmore, M.; and Cooper, A.M. The relationship between syndrome and personality disorder in DSM-III: Experience with 2,462 patients. *Am J Psychiatry* 142:207-212, 1985.

Kosten, T.A.; Kosten, T.R.; and Rounsaville, B.J. Personality disorders in opiate addicts show prognostic specificity. *J Subst Abuse Treat* 6:163-168, 1989.

LaTorre, R.A. Pretherapy role induction procedures. *Can Psychol Rev* 8:308-320, 1977.

Linehan, M.M. *Cognitive Behavioral Therapy of Borderline Personality Disorder.* New York: Guilford Press, 1993a.

Linehan, M.M. *The Skills Training Manual for Treating Borderline Personality Disorder.* New York: Guilford Press, 1993b.

Linehan, M.M. Dialectical behavior therapy for treatment of borderline personality disorder: Implications for the treatment of substance abuse. In: Onken, L.S.; Blaine, J.D.; and Boren, J.J., eds. *Behavioral Treatments for Drug Abuse and Dependence.* National Institute on Drug Abuse Research Monograph 137. NIH Pub. No. 93-3684. Washington, DC: Supt. of Docs., U.S. Govt. Print. Off., 1993c.

Linehan, M.M.; Armstrong, H.E.; Suarez, A.; Allmon, D.; and Heard, H.L. Cognitive-behavioral treatment of chronically parasuicidal borderline patients. *Arch Gen Psych* 48:1660-1064, 1991.

Linehan, M.M.; Heard, H.E.; and Armstrong, H.E. Naturalistic follow-up of a behavioral treatment for chronically suicidal borderline patients. *Arch Gen Psych,* in press-a.

Linehan, M.M.; Tutek, D.A.; Heard, H.L.; and Armstrong, H.E. Cognitive behavioral treatment of chronically parasuicidal borderline patients: Interpersonal outcomes. *Am J Psychiatry,* in press-b.

Matas, M.; Staley, D.; and Griffin, W. A profile of the noncompliant patient: A thirty month review of outpatient psychiatry referrals. Gen *Hosp Psychiatry* 14:124-130, 1992.

McCann, J.T.; Flynn, P.M.; and Gersh, D.M. MCMI-II diagnosis of borderline personality disorder: Base rates versus prototypic items. *J Pers Assess* 58:105-114, 1992.

Nace, E.P.; Saxon, J.J.; and Shore, N. A comparison of borderline and nonborderline alcoholic patients. *Arch Gen Psych* 40:54-60, 1983.

Pitts, W.M.; Gustin, Q.L.; Mitchell, C.; and Snyder, S. MMPI critical item characteristics of the DSM-III borderline personality disorder. *J Nerv Ment Dis* 173:628-631, 1985.

Sparr, L.F.; Moffitt, M.C.; and Ward, M.F. Missed psychiatric appointments: Who returned and who stays away. *Am J Psychiatry* 150:801-805, 1993.

Tousignant, M., and Kovess, V. Borderline traits among community alcoholics and problem-drinkers: Rural-urban differences. *Can J Psychiatry* 34:796-799, 1989.

Vaglum, S., and Vaglum, P. Borderline and other mental disorders in alcoholic female psychiatric patients: A case control study. *Psychopharmacology* 18:50-60, 1985.

Waldinger, R.J., and Frank, A.F. Clinicians' experiences in combining medication and psychotherapy in medication and psychotherapy in the treatment of borderline patients. *Hosp Community Psychiatry* 40:712-718, 1989.

Zanarini, M.C.; Gunderson, J.G.; Frankenburg, F.R.; and Chancey, D.L. The revised diagnostic interview for borderlines: Discriminating BPD from other axis II disorders. *J Pers Disord* 3: 10-18, 1989.

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Integration of Behavioral and Pharmacological Treatments for Panic Disorder: Implications for the Treatment of Substance Dependence

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INTRODUCTION

To illustrate possible strategies for integrating behavioral and pharmacological interventions for the treatment of substance abuse, this chapter considers similar issues in the conceptualization and treatment of panic disorder. Significant advances in the treatment of panic disorder have been achieved through basic research, analog studies, and treatment outcome investigations. The recent National Institutes of Health (NIH) Consensus Development Conference (National Institutes of Health 1991) on the treatment of panic disorder identified both pharmacologic and cognitive behavioral interventions as effective treatment strategies. Difficulties with side effects and treatment discontinuation were cited as limitations of pharmacologic interventions. In contrast, brief cognitive behavioral treatments were identified as offering promising outcome in the short and long term without side effects.

Of possible pharmacotherapies for panic disorder, high-potency benzodiazepines and antidepressants have been well studied. In controlled treatment trials of the short-term efficacy of high-potency benzodiazepines, mainly alprazolam and clonazepam, panic-free rates at treatment endpoint range from 48 percent to 70 percent (Ballenger et al. 1988; Cross-National Collaborative Panic Study 1992; Tesar et al. 1991). Placebo response rates have ranged from 14 percent to 50 percent in these studies. Patients treated with imipramine, the most commonly studied tricyclic antidepressant, achieved comparable panic-free rates as patients treated with benzodiazepines (Cross-National Collaborative Panic Study 1992), although in treatment trials problems with tolerability of imipramine have led to large dropout rates, often in the range of 30 percent to 35 percent (Aronson 1987; Cross-National Collaborative Panic

Study 1992; National Institutes of Health 1991). In clinical practice, however, gradual dosage titration has been associated with greater tolerance of treatment (Pollack and Rosenbaum 1988). Monoamine oxidase inhibitors (MAOIs) are considered among the most comprehensively effective pharmacologic agents for the treatment of panic disorder and its complications, although their use is associated with a number of treatment-emergent side effects (Sheehan et al. 1980). Further, patients may be daunted by the dietary proscriptions and fears of hypertensive crises.

In comparison to pharmacotherapy, studies of short-term treatment efficacy for behavior therapy report response rates often above 80 percent (Barlow et al. 1989; Beck et al. 1992; Clark 1986; Michelson et al. 1990). In one study directly comparing alprazolam treatment to behavior therapy, a 50 percent panic-free rate was found for alprazolam compared to an 86 percent panic-free rate for behavior therapy (Klosko et al. 1990). Long-term followup studies of cognitive-behavioral therapy also indicate maintenance of treatment gains. In a recent trial of panic disorder patients treated with cognitive behavioral therapy, 81 percent remained panic-free at a 2-year followup (Craske et al. 1991). These rates compare favorably to long-term followup studies of medication-treated patients that have found 50 percent to 80 percent of patients remain symptomatic and 40 percent of patients continued to have panic attacks at followup periods ranging from 1.5 to 6 years (Nagy et al. 1989; Noyes et al. 1989; Pollack et al. 1994).

In summary, outcome studies of cognitive behavioral and pharmacologic treatments indicate that these treatments are superior to wait-list control groups or placebo treatment, and results to date indicate that cognitive behavioral treatments may provide a higher panic-free rate and longer maintenance of treatment gains in some groups of patients. To understand how cognitive behavioral treatments differ from pharmacologic treatment, and how these treatment strategies may be combined, it is important to understand the model of panic disorder on which these treatments are based. Cognitive behavioral interventions follow naturally from this model. The model also highlights elements of panic disorder that may be untreated by medication interventions and may be especially amenable to cognitive behavioral strategies.

A COGNITIVE BEHAVIORAL MODEL OF PANIC DISORDER

Cognitive behavioral models of panic disorder have benefited from an extensive research base that includes both clinical and analog studies. Cognitive behavioral accounts of panic disorder (Barlow 1988; Beck et al. 1985; Clark 1986; Goldstein and Chambless 1978; McNally 1990) propose that panic disorder is maintained by a "fear of fear" cycle in which patients learn to fear the bodily sensations of anxiety itself, In these accounts, panic episodes are viewed in the context of the organism's emergency response to danger. Biological differences in emotional reactivity may facilitate this response, where some individuals may have a lower threshold for autonomic arousal and/or the full firing of the alarm reaction. However, it is the overattention to and catastrophic misinterpretations of somatic sensations of anxiety that is thought to maintain the disorder.

Under conditions of actual danger cueing the alarm reaction, attention is typically focused on the source of the danger (e.g., focus on the physical danger from a near car accident) rather than the sensations themselves. In contrast, initial panic attacks often occur at a time of stress, but when no physical danger is apparent. When the alarm reaction fires in the absence of external danger, individuals often devote attention to the bodily reaction itself. For patients with panic disorder, the interpretations of these bodily sensations include some of the most fearsome events imaginable, typically fears of death or disability triggered by the panic sensations ("I'm about to have a stroke"; "I am having a nervous breakdown") or the perceived consequences of these sensations ("I am about to lose control and everyone will notice"). These catastrophic thoughts become cues for reactivation of the alarm response. With each subsequent panic episode, the alarm response becomes more firmly linked with these catastrophic cognitions and the intensification of the anxiety reaction. Over time, patients may respond automatically with panic to feared sensations without attention to mediating cognitions.

The fear-of-fear cycle can be intensified by anticipatory anxiety, which increases arousal and primes the body for another emergency response. Vigilance to feared somatic sensations ensures that subtle sensations are noticed, essentially providing more phobic stimuli that may be interpreted catastrophically. Together, vigilance to and catastrophic misinterpretation of somatic sensation help feed the disorder, such that once-innocuous stimuli become cues for panic episodes. For example, patients frequently report fear or panic in response to subtle body

sensations such as the increased heart rate that may occur after climbing stairs or drinking coffee. Avoidance of physical activity or caffeine may result. This same process accounts for the development of agoraphobic avoidance, where the avoidance is of situations where panic attacks may occur. Typically the strongest avoidance is of those situations where perceived coping responses (including escape) are blocked. The complete fear-of-fear cycle is represented in figure 1.

For the cognitive behavioral therapist, the treatment of panic disorder becomes a task of eliminating the fear-of-fear cycle. For this task, the clinician is faced with a number of complementary problems including: (1) the patient's vigilance to bodily sensations, (2) the catastrophic interpretations of these sensations, (3) conditioned fear reactions to these sensations, (4) the development of chronic arousal, and (5) the emergence of agoraphobic avoidance and other maladaptive coping techniques. The challenge of treating panic disorder thus becomes a case of eliminating these five problems.

Current cognitive behavioral treatments commonly utilize five components of treatment. The first is an informational component that provides an overview of the fear-of-fear cycle and offers a basis for understanding the patterns inherent to the disorder and a rationale for treatment interventions. The second component is the cognitive interventions that address the role of catastrophic thoughts and help patients eliminate these thoughts by providing cognitive restructuring and self-coaching strategies (Barlow and Craske 1989; Beck et al. 1985). The third component is exposure to the somatic sensations of anxiety associated with panic. This exposure (interoceptive exposure) is achieved through a variety of activities such as hyperventilation, running in place, and spinning in a chair (Barlow and Craske 1989). Interoceptive exposure provides an opportunity both to elicit catastrophic cognitions and rehearse coping strategies, but the primary aim is to promote habituation to the somatic sensations themselves. The fourth component is the somatic management skills designed to eliminate bodily reactions that may increase panic sensations. In particular, these strategies are aimed at providing breathing retraining using diaphragmatic and slow breathing skills, and decreasing muscle tension using progressive muscle relaxation procedures. A final component is exposure to avoided situations. This in vivo exposure is associated with effective treatment of agoraphobia by helping patients eliminate their feared reactions to avoided situations. As noted above, short-term treatments using these interventions, typically 10 to 15 sessions, are associated with panic-free

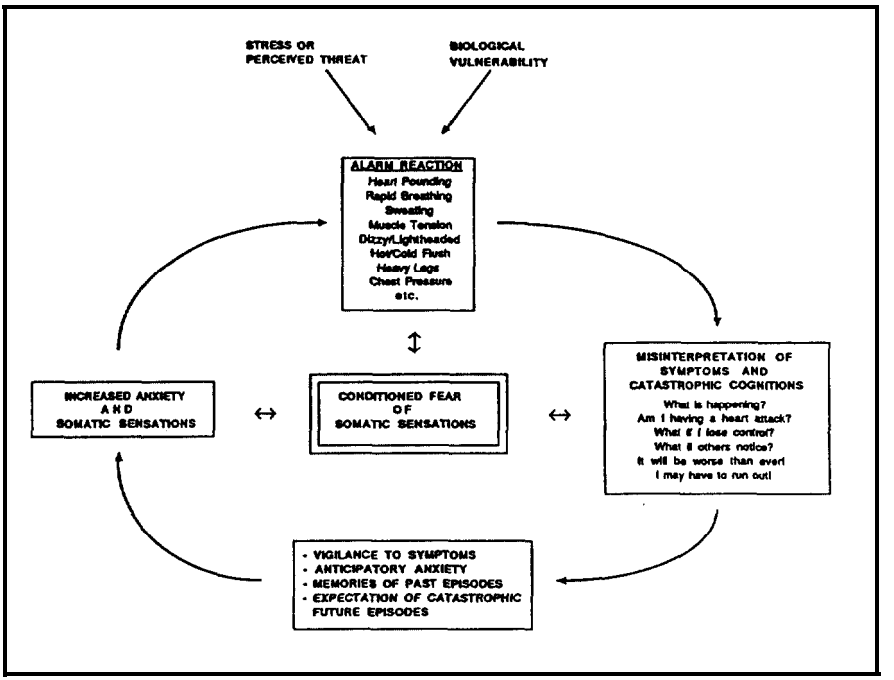

FIGURE 1. *Cognitive behavioral model of panic disorder (Reprinted from Otto et al. 1992, p. 12.5).*

rates above 80 percent, and maintenance of these gains at 2-year followup (Craske et al. 1991).

FEAR-OF-FEAR AND PHARMACOLOGIC TREATMENT

To understand the interaction between pharmacologic and behavioral treatment, it is helpful to examine the elements of the fear-of-fear cycle that are affected by medications. From a cognitive behavioral perspective, several actions of pharmacotherapy are likely. First, pharmacotherapy may block generalized anxiety. A decrease in generalized anxiety is important because, according to the fear-of-fear model, anticipatory anxiety is a cue for vigilance to somatic sensations and catastrophic cognitions and is the source of somatic sensations of anxiety to be noticed. Second, pharmacotherapy raises the threshold for the alarm reaction itself, making it more difficult for patients to have a panic attack. Finally, pharmacotherapy may operate by providing a conditioned safety cue. That is, patients know that they are on their

medication and that the likelihood of panic is reduced. This knowledge may have direct effects on the vigilance to bodily sensations and the likelihood of catastrophic cognitions, thereby further decreasing the likelihood of panic. The sometimes dramatic effects of safety cues on panic may be reflected in the high placebo response rates (30 to 50 percent) found in controlled studies (Ballenger et al. 1988; Cross-National Collaborative Panic Study 1992).

Conditioned safety cue effects may be somewhat greater with benzodiazepines relative to other medications because patients experience a rapid anxiolytic effect after medication ingestion. This conditioned safety cue effect may be further emphasized by difficulties with interdose rebound anxiety, as patients experience the return of anxiety a few hours after their last benzodiazepine dose, particularly with shorter acting agents (Pollack and Rosenbaum 1988). High-potency benzodiazepines may provide the strongest learning of safety cues for medication, but patients also report a sense of safety on antidepressant treatments.

Although these hypothesized actions of pharmacotherapy are enough to provide panic cessation in approximately 50 percent to 70 percent of treated patients, these actions do not focus directly on elimination of fearful reactions to somatic sensations. Hence, patients may continue a pattern of vigilance and fear of these sensations, making it difficult for pharmacological treatment to fully eliminate the disorder. One clear area for the interaction between cognitive behavioral therapy and pharmacotherapy, then, is the use of cognitive behavioral techniques, particularly interoceptive exposure and cognitive restructuring, to eliminate untreated “fear of fear” in patients undergoing pharmacotherapy. In the next several sections, this type of treatment is detailed as it is applied to medication treatment-resistant patients, patients undergoing discontinuation of pharmacotherapy, and finally to programs combining pharmacotherapy and behavior therapy from the initiation of treatment.

COGNITIVE BEHAVIOR THERAPY FOR TREATMENT-REFRACTORY PANIC DISORDER PATIENTS

As noted above, followup studies of patients with panic disorder who are treated with tricyclic antidepressants and high-potency benzodiazepines indicate that many patients remain symptomatic over the long term. Studies utilizing assessments ranging from 1.5 years to 6 years after the

initiation of medication treatment indicate that the majority of patients remain on medication and 50 percent to 86 percent continue to be symptomatic (Nagy et al. 1989; Noyes et al. 1989; Pollack et al. 1993). As such, many patients undergoing pharmacotherapy may require additional interventions to achieve full remission of their disorder.

In a recent study of patients with panic disorder who were treatment refractory or relatively treatment refractory, the authors found that cognitive behavioral strategies were effective in improving treatment outcome (Pollack et al. 1994). Subjects for the study were 15 consecutive patients with panic disorder and agoraphobia who were referred because of incomplete response to pharmacotherapy; eight of these patients were defined as relatively refractory. Reasons for inadequate treatment included: (1) the patient's desire to control symptoms without medication, (2) physician or patient concern about withdrawal or addiction, (3) physician opinion that the patient had received an adequate trial, or (4) medication side effects. The remaining patients had received a fully adequate trial but failed to respond satisfactorily. The panic disorder was the primary disorder under treatment, but patients in the study had a wide range of co-morbid anxiety and affective disorders, including one patient with a past history of mania.

All patients were treated in a 12-week cognitive behavioral therapy group modeled on the treatment program described by Barlow and Craske (1989). Interventions in the group included the interoceptive exposure, cognitive restructuring, somatic management skills, and in vivo exposure interventions described above. Results at the endpoint of treatment and at several months posttreatment indicated substantial improvement, with significant decreases in both global severity of the disorder and panic frequency. Three patients (20 percent) also discontinued part or all of their medication treatment during the course of behavioral treatment.

The results of this open trial of behavior therapy for medication-resistant and relatively resistant patients are consistent with previous studies demonstrating an additive effect when pharmacotherapy and behavioral therapy are combined. For example, Mavissakalian (1990) found that the addition of exposure-based behavior therapy after an initial 8-week trial of imipramine resulted in continued improvement in anxiety, depression, and phobic avoidance. Other studies indicate that the combination of imipramine treatment and exposure is superior to imipramine treatment alone (Mavissakalian et al. 1983; Telch et al. 1985). When combined

treatment is compared to in vivo exposure alone, imipramine treatment appears to enhance the effects of exposure acutely, but not at followup evaluations (Mavissakalian and Michelson 1986a, 1986b; Telch et al. 1985). However, a recent study by Marks and colleagues (1993a) examining the combination of exposure treatment and benzodiazepine treatment found no incremental benefit when alprazolam was combined with exposure treatment for patients with panic disorder and significant agoraphobic avoidance. In addition, alprazolam treatment appeared to hinder the maintenance of gains resulting from exposure treatment when the alprazolam was discontinued. Notably, the Marks and colleagues (1993a) protocol did not include a specialized program for the discontinuation of alprazolam treatment, nor did it include interoceptive exposure and cognitive restructuring treatment elements.

COGNITIVE BEHAVIORAL THERAPY FOR BENZODIAZEPINE DISCONTINUATION IN PATIENTS WITH PANIC DISORDER

Difficulties with discontinuing benzodiazepine treatment have been well-documented. Discontinuation distress occurs with both short and long half-life benzodiazepines, even when slowly tapered (Fyer et al. 1987; Mellman and Uhde 1986; Rickels et al. 1990; Roy-Byrne and Hommer 1988). Patients with panic disorder often have marked difficulties discontinuing benzodiazepines. For example, Noyes and associates (1991) found that panic attacks recurred in 74 percent of patients undergoing discontinuation of their alprazolam treatment. Of these patients, 64 percent were not successful in the discontinuation attempt, and 60 percent experienced symptoms during discontinuation that were equal to or more severe than experienced prior to treatment. Similar difficulties have been found for the discontinuation of long half-life agents in patients with panic disorder (Noyes et al. 1991; Rickels et al. 1990).

A cognitive behavioral account of discontinuation difficulties in patients with panic disorder has been reported (Otto et al. 1992). The authors hypothesize that difficulties during benzodiazepine discontinuation occur because patients are exposed to anxiety sensations at a time when they fear a return of the disorder and are especially vigilant to symptoms due to removal of the conditioned safety cue of medication. Benzodiazepine withdrawal symptoms mimic many of the symptoms of panic disorder (Roy-Byrne and Hommer 1988), and hence the medication taper ensures an exacerbation of somatic sensations of anxiety at a time when patients

are fearing this increase. Because of untreated fears of these sensations and worries that these sensations represent a return of panic disorder, patients frequently respond to these sensations with catastrophic interpretations and fear, contributing to an increase in anxiety and panic episodes.

Given the model of discontinuation difficulties, it has been hypothesized that an effective behavioral treatment for benzodiazepine withdrawal must:

1. Decrease conditioned fears of somatic sensations and the tendency to catastrophically misinterpret these sensations.

2. Provide patients with coping skills for managing the severity of panic sensations.

3. Provide patients with skills for minimizing withdrawal symptoms (Otto et al. 1992, p. 127).

In a test of the authors' hypotheses, a treatment for benzodiazepine discontinuation that incorporated the informational, cognitive restructuring, interoceptive exposure, and somatic management skills were designed, as discussed above. The authors studied 33 outpatients treated for panic disorder who had been treated with either alprazolam or clonazepam for a minimum of 6 months (Otto et al. 1993). These patients were seeking help in discontinuing their benzodiazepine treatment and were randomly assigned to one of two taper conditions: a slow-taper condition with physician support, or a slow-taper condition with support plus 10 sessions of group cognitive behavioral therapy. Consistent with previous studies high rates of discontinuation failure in patients undergoing the slow-taper-alone program were found. Seventy-five percent of these patients were unable to discontinue their medication on schedule. In contrast, 76 percent of patients receiving the adjunctive cognitive behavioral treatment were successful in achieving medication discontinuation. In addition, patients successfully discontinuing their medication had lower levels of distress than they had at pretreatment. Three months postdiscontinuation followup indicated that most patients in the cognitive behavioral program (77 percent) remained benzodiazepine-free. Also, two of three patients who crossed over to the cognitive behavioral program from the slow-taper-alone program achieved successful benzodiazepine discontinuation on schedule. In

summary, it appears that a brief focused trial of cognitive behavioral treatment is effective in aiding benzodiazepine discontinuation.

The authors believe that the most important elements of this program were the interoceptive and cognitive restructuring components. Interoceptive exposure was designed to treat the fear-of-fear reaction to somatic sensations associated with panic and to help treat anxiogenic reactions to somatic sensations that may arise due to medication discontinuation. In addition to trying to eliminate catastrophic interpretations of symptoms, cognitive restructuring interventions were used to help patients reconceptualize their withdrawal symptoms and mobilize preexisting coping efforts. One particular strategy was to have patients identify their reactions to the symptoms experienced when having the flu. Patients reported responding to flu sensations without anxiety or fear; they accepted that uncomfortable sensations were part of the flu and went about their daily activities as best they could. Patients were then asked to apply this familiar skill to the bodily discomfort they were experiencing during the benzodiazepine taper process. In short, they were asked to use existing skills to be more comfortable with their taper-induced "benzodiazepine flu." These procedures are illustrated in greater detail in the authors' treatment manuals (Otto et al., in press; Otto et al. 1994), but this example is illustrative of the use of cognitive interventions to mobilize preexisting coping skills to aid in medication discontinuation. The combination of these cognitive interventions with interoceptive exposure procedures ensures that patients have in-session training in reacting differently to somatic sensations associated with anxiety, panic, and withdrawal symptoms.

Similar to the program for treatment-refractory patients, these interventions were preceded by a significant informational component. Discontinuation difficulties were explained in terms of the fear-of-fear model, and compensatory interventions also were outlined in ten-ns of this model. Hence, prior to initiation of medication taper, patients had a model of the action of their medications, the alternative interventions offered by cognitive behavioral therapy, the symptoms that may be encountered during medication taper, and the types of skills that will be developed for coping with these sensations and the underlying disorder. The authors believe this informational component increased comfort and compliance with cognitive behavioral treatment and the discontinuation procedures. Findings of marked efficacy for the discontinuation program encourage application of these interventions to other drug discontinuation

programs where taper-associated symptoms result in significant discontinuation difficulties.

COMBINED BENZODIAZEPINE AND COGNITIVE BEHAVIORAL TREATMENTS

At present there are few studies of combined treatments using benzodiazepine and cognitive behavioral therapy. Benzodiazepine treatment has the advantage of quick onset of action (Pollack and Rosenbaum 1988), and hence one strategy for combined treatment is to use benzodiazepine treatment to help block panic attacks and anticipatory anxiety while patients are introduced to the initial skills of cognitive behavioral therapy. Cognitive behavioral therapy can then be used to help patients successfully discontinue their benzodiazepine treatment and continue to develop skills for eliminating panic disorder over the long term.

In the authors' clinic program, successful treatment of several patients using this method have been observed. To offer an understanding of the treatment process, patients were provided a behavioral model of the disorder and treatment at an early stage, and the rationale for short-term benzodiazepine treatment was presented in this context. Recently, Hegel and associates (1994) reported on a small open trial combining cognitive behavioral treatment and alprazolam treatment. In this study, 25 patients were initially treated with or switched to a panic suppression dose of alprazolam. Following a 2-week panic-free stabilization period, patients began a 12-session individual cognitive behavioral treatment program modeled after Barlow and Craske (1989). After 4 weeks of treatment, patients began a gradual tapering of alprazolam medication. Three patients were lost to followup. Of the original sample, 80 percent were panic-free at the end of the treatment period, with further improvements evident at 12 months followup, where 85 percent of patients were panic-free.

Spiegel and associates (1994) investigated combined treatment in 2 1 patients with panic disorder. Patients were first treated with a panic-suppressing dose of alprazolam and then were discontinued in a slow-taper program or in an identical-taper program plus 12 weeks of cognitive behavioral therapy. Eighty percent of taper only and 90 percent of the taper-plus-cognitive behavioral therapy patients were able to discontinue their acute alprazolam treatment, but whereas all patients in the cognitive

behavioral therapy program maintained their gains, half the subjects in the taper-only group relapsed and went back on drugs during a 6-month followup period. This study again supports the effectiveness of short-term alprazolam treatment combined with a cognitive behavioral therapy program.

These data indicate that treatments combining very short-term treatment with high-potency benzodiazepines followed by brief cognitive behavioral treatment may offer patients the best of both treatments. This brief benzodiazepine treatment offers rapid blockade of anxiety and panic, whereas the cognitive behavioral treatment is used to treat the cognitive behavioral patterns associated with the fear-of-fear cycle to aid benzodiazepine discontinuation and the maintenance of a panic-free status over the long term.

The combination of other pharmacologic interventions, (e.g., tricyclic or MAOI antidepressants) and behavior therapy may offer similar advantages, but additional research is necessary to determine whether chronic treatment with these agents is superior to behavior therapy alone for the average patient. As argued by Marks and colleagues (1993b), the success of behavior therapy for the majority of patients in treatment studies may support the initial application of behavioral treatment for most patients. Nonetheless, combined treatment may be the treatment of choice for the patients with panic disorder who do not respond to brief cognitive behavioral therapy trials or for patients who insist upon immediate medication treatment. The relative advantages of cognitive behavioral, pharmacological, or combined treatments also may change depending on the intensity of co-morbid conditions, as most treatment studies exclude patients with significant co-morbidity.

POTENTIAL PROBLEMS FOR THE COMBINATION OF COGNITIVE BEHAVIORAL THERAPY AND PHARMACOLOGIC TREATMENTS

In the above discussions of combined cognitive behavioral and pharmacological interventions, efforts have been emphasized in providing patients with a model of the disorder and treatment. Whereas this model includes assumptions of potential biological diatheses for the disorder, it implicates nonbiological factors as primary in sustaining the disorder. A potential problem for the combined treatments is conflict between models provided to patients by caregivers. Many patients

receiving medication treatment accept the implicit biological formulation that panic disorder is a manifestation of a chemical dysregulation. Correspondingly, medications are viewed as a means to correct this dysregulation. If a patient is told, for example, that panic disorder is analogous to diabetes, that both are chronic diseases, and that like the diabetic who controls the condition with insulin, the panic disorder patient must control his or her condition with medication, this conceptualization would be counterproductive to having the patient fully engage in cognitive behavioral therapy.

To address this issue in the authors' behavior therapy clinic, where inadequate responders to medication treatment are commonly referred, attention was devoted in the first treatment session to providing a broader model of the disorder. In particular, biological provocation studies have been used to support a purely biological conceptualization of panic disorder. In these studies a number of biological agents, ranging from yohimbine and lactate to carbon dioxide inhalation and caffeine, were used to provoke panic in patients with panic disorder but not in control subjects (Clark 1986). In the authors' treatment program, patients learn about these and additional studies that support psychological interpretations of this finding. These studies indicate that individuals who fear somatic sensations of anxiety respond to these procedures with anxiety and panic, regardless of a history of panic disorder or panic attacks (McNally and Lorenz 1987; Telch and Harrington 1992). Instead of sharing a common biological pathway, the most important shared characteristic of these agents may be the ability to unexpectedly induce bothersome somatic sensations (Clark 1986). Hence, findings from provocation studies that also could support a biological model of panic disorder now support a fear-of-fear model. This information is used to help patients understand some of the evidence for each model of the disorder and to prepare them for a new conceptualization of the disorder that precedes cognitive behavioral therapy. In the discontinuation program the fear-of-fear model is used to explain potential mechanisms for drug action (i.e., blocking baseline anxiety, raising the threshold for the alarm response, and providing a conditioned safety cue) and the alternative interventions to be addressed in behavior therapy (i.e., cognitive restructuring, interoceptive exposure, somatic management skills, and in vivo exposure). Patients thus have a unified model for the disorder and their past and current treatment.

To review, the goal of the presentation of these empirical findings and the model of the disorder is to help patients fully engage in cognitive

behavioral treatment. This is especially important because behavioral clinicians are offering interventions that require more effortful assimilation than taking a pill. This informational presentation also serves to educate patients about their disorder and the purpose of each intervention so that they can be better prepared to guide their own interventions during and after the treatment period. It is important to underscore the significance of information interventions at the outset of treatment and clear communication between behaviorally and pharmacologically oriented caregivers throughout the treatment process to ensure that patients receive consistent messages about the treatments they are receiving.

A second concern for the combination of behavioral and pharmacologic treatments is the use of a dosing schedule that avoids pill taking as an immediate coping response to panic attacks. Patients in behavioral treatment must learn alternative responses to anticipatory anxiety and panic attacks if treatment is to be effective. "As needed" (PRN) use of benzodiazepine medications could potentially interfere with this process. Thus, the use of fixed dosing schedules and the substitution of behavioral strategies for PRN dosages is important for the transition to behavioral treatment of panic disorder.

More traditional concerns about the combination of pharmacologic and behavioral treatments focus on state-dependent learning and the attribution of therapeutic gains to medications rather than skill acquisition (Barlow 1988; Marks et al. 1993a). Concerns about state-dependent learning focus on whether skills learned while on medication will disappear when medications are withdrawn (Bouton et al. 1990). The authors' experience with benzodiazepine discontinuation suggests that state-dependent learning is not a problem when behavioral skills are rehearsed over the course of discontinuation. This rehearsal requires that patients have experience with behavioral skills in the absence of drug treatment.

As noted by Barlow (1988), the attribution of treatment efficacy to other sources is not limited to medications; patients may also attribute early treatment effects to the presence of their therapist, to luck, or to any of a number of safety cues in addition to medications. The attribution of treatment effects to other sources can be eliminated by selection of appropriate homework assignments where patients are placed in situations where success with their new skills occurs independently of the therapist or other perceived aid. In relation to medication treatment, the

use of an organized discontinuation program or close monitoring of the effects of behavior therapy (while medication treatment is held constant) can be used to help patients identify the source of their progress. Self-monitoring diaries are especially useful for this purpose.

Finally, concerns have been raised whether pharmacological treatments interfere with the actions of behavioral treatment. One proposed action, termed biological "toughening up," is the desensitization of the central nervous system resulting from repeated exposure to anxiogenic stimuli; benzodiazepines are hypothesized to interfere with this process (Barlow 1988). Tricyclic antidepressants have drawn less concern, especially as there is some evidence that they may provide short-term potentiation of exposure treatment (Mavissakalian and Michelson 1986a, 1986b; Telch et al. 1985). Although individual doses of benzodiazepines may have a beneficial effect on exposure therapy under select conditions (Marks et al. 1972), Marks and associates (1993a) have provided recent evidence that brief benzodiazepine treatment may hinder rather than help exposure-based treatment, at least in patients with severe agoraphobia who did not have the benefit of a behavioral discontinuation program or interoceptive exposure procedures. In addition, research needs to address whether the authors' pilot program combining cognitive behavioral therapy with brief benzodiazepine treatment for patients seeking immediate relief really offers the "best of both worlds" as has been proposed. It is clear that adding behavior therapy to medication treatment offers significant benefit. Research must now address which patients benefit from each treatment individually and which patients may require combined treatment for maximal improvement.

APPLICATION OF FINDINGS TO ISSUES OF DRUG DEPENDENCY

The combination of pharmacotherapy and behavior therapy has been described as it is applied to treatment-resistant patients with panic disorder, patients requiring medication discontinuation, and as a combined intervention with short-term benzodiazepine treatment. Although research investigating combined pharmacologic and cognitive-behavioral treatment is still in its infancy, several lessons can be learned from the research on panic disorder conducted thus far. These lessons include the use of (1) a clear model to guide treatment and combinations of treatments, (2) a clear rationale for treatment interventions, (3) a focus on skill acquisition with specific practice of skills in relevant circum-

stances, and (4) exposure procedures for interoceptive cues. Each of these lessons has potential application to the treatment of drug dependency, with particular application to the design of combined treatments, the addition of behavior therapy to aid in minimizing drug withdrawal effects, and in maintaining effective outcome when tapering pharmacotherapy.

Use of an Empirically Supported Model to Guide Treatment

An advantage of a comprehensive model is that it suggests treatment interventions for elements of the disorder not addressed by medication. By identifying what is and is not addressed by each intervention, clinicians can choose the best from each treatment. In the area of panic disorder, this strategy was exemplified by programs targeting patients with panic disorder who were not fully responsive to medication, were undergoing medication discontinuation, or who were starting treatment. In each case, untreated fears of somatic sensations were a primary target of treatment, following the notion that this fear and associated behavior patterns remained untreated for many patients undergoing pharmacotherapy. In the area of drug dependence, the application of combined treatments may be aided by a similar conceptual model: a model that identifies the nature of the disorder and the type of change that results from pharmacologic and cognitive behavioral interventions. With specification of the elements of the disorder altered by one set of interventions, combined interventions can be structured to best "cover" the range of factors maintaining the substance abuse.

Improving Motivation and Compliance: The Value of Informational Interventions

These authors repeatedly identified the value of informational interventions for patients. By specifying the elements of the disorder that may be treated by each form of intervention and the purpose of each intervention, active participation in combined treatment may be maximized. This intervention has been identified as important when cognitive behavioral therapy was being added to existing pharmacotherapy, when pharmacotherapy was being replaced by a short-term cognitive behavioral therapy program, and when pharmacotherapy and behavior therapy were combined at treatment onset. This informational component of treatment may be especially important for the treatment of drug dependence. Attrition and compliance is a major issue for the treatment of drug dependence (e.g., Rounsaville et al. 1983;

Sanchez-Craig et al. 1987, pp. 287-331), and like patients in the authors' discontinuation program, patients treated for substance abuse must learn to develop and substitute behavioral skills for previous drug-taking behavior. A clear rationale for the exact benefits to be received by this substitution of behavior therapy for drug-taking behavior may aid this process.

A Focus on Skill Acquisition in Realistic Circumstances

The focus on skill acquisition represents a third component of the cognitive behavioral approach toward panic disorder that may offer benefit to the treatment of substance abuse. In the cognitive behavioral treatment of panic disorder, patients are provided with an abundance of training in developing skills to eliminate aspects of the panic cycle. For example, they are provided with breathing retraining and muscle relaxation skills to help ameliorate the intensity of their symptoms and to help stop anxiogenic reactions to initial anxiety or withdrawal sensations. When possible, patients are helped to draw upon existing skills for maximizing cognitive interventions. For example, in the benzodiazepine discontinuation program the concept of "benzodiazepine flu" is introduced to help patients cope with withdrawal symptoms. Finally, newer cognitive behavioral programs ensure that patients have direct practice with eliminating panic cycles by exposing them to feared bodily sensations in interoceptive exposure procedures. In all cases, these strategies were practiced independently from the use of medications and, where relevant, during the process of medication discontinuation. This practice in both medicated and nonmedicated states, as well as under conditions of induced anxiety, help circumvent issues of state-dependent learning. The treatment of drug dependence may benefit from similar strategies (Niaura et al. 1988), where component skills are identified and rehearsed before and during discontinuation and maintenance phases as part of preparation for high-risk situations.

Treatment Interventions for Interoceptive Cues

The final lesson from the cognitive behavioral treatment of panic disorder is the usefulness of interoceptive exposure techniques. In the authors' treatment for benzodiazepine discontinuation, interoceptive exposure techniques were used to help patients reduce their fear of somatic sensations of both anxiety and withdrawal and to develop skills for coping with these sensations. Patients were exposed to interoceptive sensations during the treatment session, providing them with the

opportunity for habituation and an opportunity to rehearse cognitive and behavioral skills. Patients thus had existing skills and experiences when similar interoceptive cues were experienced during the course of benzodiazepine withdrawal or when anxiety sensations were encountered thereafter.

Treatments of drug dependency have recognized various contextual cues for drug-seeking or drug-taking behaviors (Niaura et al., 1988; Rohsenow et al. 1990-1991). Although there has been clear identification that some important cues are interoceptive rather than external contextual cues (Marlatt and Gordon 1978, pp. 410-452; O'Connell and Martin 1987), cue exposure treatments have focused primarily on the external contextual cues surrounding drug use (O'Brien et al. 1990; Powell et al. 1990; Rohsenow et al. 1990-1991). This focus on environmental cues is similar to older treatments of panic disorder and agoraphobia that targeted in vivo exposure rather than exposure to the somatic sensations of anxiety. In parallel to advances in the treatment of panic disorder, the treatment of substance abuse also may benefit from interoceptive exposure techniques.

Extending these procedures to the treatment of substance abuse, interoceptive exposure procedures could be used to help patients achieve initial drug discontinuation and to resist cues for relapse. Novel interoceptive exposure procedures (e.g., mood induction) may be needed for select affective cues, but in many cases similar procedures to those described by Barlow and Craske (1989) may be appropriate. For example, George and colleagues (1988) found that alcohol withdrawal is not discriminated from panic sensations in individuals who have both alcohol dependence and panic disorder. Furthermore, fears of somatic sensations occur at moderate to high levels in substance-abusing populations. In particular, scores on one measure of fear of anxiety symptoms, the Anxiety Sensitivity Index, have been found to be elevated in samples of alcoholics (McNally et al. 1987) and in opiate-dependent patients (Pollack et al., unpublished data). If one component of ongoing substance abuse is the "self-medication" of disturbing interoceptive cues resulting from withdrawal, anxiety, or stress, then interoceptive exposure techniques may offer an additional means to intervene with substance-abusing populations. The authors' clinical research group is now investigating the application of these interventions to patients undergoing opiate withdrawal. Similar interventions may be of use for nicotine and alcohol withdrawal.

CONCLUSION

Overall, the cognitive behavioral treatment of panic disorder offers a number of important insights that may be applied to issues of combined treatment of substance abuse. These lessons include the development of a clear model of the disorder to guide treatments and help patients understand and comply with the interventions, ongoing practice of skills to improve coping with manifestations of the disorder, and the use of interoceptive techniques to help substance-dependent patients cope with withdrawal sensations they may experience as they try to taper and discontinue their substance use. Application of these methods may lead to further advances in the treatment of substance abuse. More generally, the opportunity for professionals in two distinct areas of study to review one another's work and findings is encouraged as a method to increase the effectiveness of research in both areas of study. The organizers of the NIDA Technical Update Conferences should be commended for their efforts in encouraging this process.

REFERENCES

Aronson, T.A. A naturalistic study of imipramine in panic disorder and agoraphobia. *Am J Psychiatry* 144(8):1014-1019, 1987.

Ballenger, J.; Burrows, G.; DuPont, R.; and Lesser, I.M. Alprazolam in panic disorder and agoraphobia: Results from a multicenter trial: I. Efficacy in short-term treatment. *Arch Gen Psychiatry* 45(5):413-422, 1988.

Barlow, D.H. *Anxiety and Its Disorders: The Nature and Treatment of Anxiety and Panic.* New York: Guilford Press, 1988.

Barlow, D.H., and Craske, M.G. *Mastery of Your Anxiety and Panic.* Albany, NY: Graywind Publications, 1989.

Barlow, D.H.; Craske, M.G.; Cemy, J.A.; and Klosko, J.S. Behavioral treatment of panic disorder. *Behav Ther* 20(2):261-282, 1989.

Beck, A.T.; Emery, G.; and Greenberg, R.L. *Anxiety Disorders and Phobias: A Cognitive Perspective.* New York: Basic Books, 1985.

Beck, A.T.; Sokol, L.; Clark, D.A.; Berchick, R.; and Wright, F. A crossover study of focused cognitive therapy for panic disorder. *Am J Psychiatry* 149(6):778-783, 1992.

Bouton, M.E.; Kenney, F.A.; and Rosenbard, C. State dependent fear extinction with two benzodiazepine tranquilizers. *Behav Neurosci* 104(1):44-55, 1990.

Clark, D.M. A cognitive approach to panic. *Behav Res Ther* 24(4):461-470, 1986.

Craske, M.G.; Brown, T.A.; and Barlow, D.H. Behavioral treatment of panic: A two year follow-up. *Behav Ther* 22(3):289-304, 1991.

Cross-National Collaborative Panic Study, Second Phase Investigators. Drug treatment of panic disorder: Comparative efficacy of alprazolam, imipramine, and placebo. *Br J Psychiatry* 160:191-202, 1992.

Fyer, A.J.; Liebowitz, M.R.; Gorman, J.M.; Campeas, R.; Levin, A.; Davies, SO.; Goetz, D.; and Klein, D.F. Discontinuation of alprazolam treatment in panic patients. *Am J Psychiatry* 144:303-308, 1987.

George, D.T.; Zerby, A.; Noble, S.; and Nutt, D.J. Panic attacks and alcohol withdrawal: Can subjects differentiate the symptoms? *Biol Psychiatry* 24:240-243, 1988.

Goldstein, A.J., and Chambless, D.L. A reanalysis of agoraphobia. *Behav Ther* 9(1):47-59, 1978.

Hegel, M.T.; Ravaris, C.L.; Ahles, T.A. Combined cognitive-behavioral and time-limited Alprazolam treatment of panic disorder. *Behav Ther* 25:183-195, 1994.

Klosko, J.S.; Barlow, D.H.; Tassinari, R.B.; and Cemy, J.A. Comparison of alprazolam and behavior therapy in the treatment of panic disorder. *J Consult Clin Psychol* 58(1):77-84, 1990.

Marks, I.M.; Swinson, R.P.; Basoglu, M.; Kuch, K.; Noshirvani, H.; O'Sullivan, G.; Lelliott, P.T.; Kirby, M.; McNamee, G.; Sengun, S.; and Wickwire, K. Alprazolam and exposure alone and combined in panic disorder with agoraphobia: A controlled study in London and Toronto. *Br J Psychiatry* 162:776-787, 1993a.

Marks, I.M.; Swinson, R.P.; Basoglu, M.; Noshirvani, H.; Kuch, K.; O'Sullivan, G.; Lelliott, P.T.; and Wickwire, K. Reply to comment on the London/Toronto study. *Br J Psychiatry* 162:790-794, 1993b.

Marks, I.M.; Viswanathan, R.; Lipsedge, M.D.; and Gardner, R. Enhanced relief of phobias by flooding during waning diazepam effect. *Br J Psychiatry* 121:493-505, 1972.

Marlatt, G.A., and Gordon, J.R. Determinants of relapse: Implications for the maintenance of behavior change. In: Davidson, P.O., and Davidson, S.M., eds. *Behavioral Medicine: Changing Health Lifestyles.* New York: Brunner/Mazel, 1978. pp. 410-452.

Mavissakalian, M. Sequential combination of imipramine and self-directed exposure in the treatment of panic disorder with agoraphobia. *J Clin Psychiatry* 51(5):184-188, 1990.

Mavissakalian, M.; Michelson, L.; and Dealy, R.S. Pharmacological treatment of agoraphobia: Imipramine versus imipramine with programmed practice. *Br J Psychiatry* 143:348-355, 1983.

Mavissakalian, M., and Michelson, L. Agoraphobia: Relative and combined effectiveness of therapist-assisted in vivo exposure and imipramine. *J Clin Psychiatry* 47(3):117-122, 1986a.

Mavissakalian, M., and Michelson, L. Two year follow up of exposure in imipramine treatment of agoraphobia. *Am J Psychiatry* 143(9):1106-1112, 1986b.

McNally, R.J. Psychological approaches to panic disorder: A review. *Psychol Bull* 108(3):403-419, 1990.

McNally, R.J., and Lorenz, M. Anxiety sensitivity in agoraphobics. *J Behav Ther Exp Psychiatry* 18(1):3-11, 1987.

McNally, R.J.; Luedke, D.L.; Besyner, J.K.; Peterson, R.A.; Bohn, K.; and Lips, O.J. Sensitivity to stress-relevant stimuli in posttraumatic stress disorder. *J Anx Disord* 1(2):105-116, 1987.

Mellman, T.A., and Uhde, T.W. Withdrawal syndrome with gradual tapering of alprazolam. *Am J Psychiatry* 11(143):1464-1466, 1986.

Michelson, L.; Marchione, K.; Greenwald, M.; Glanz, L.; Testa, S.; and Marchione, N. Panic disorder: Cognitive-behavioral treatment. *Behav Res Ther* 28(2):141-151, 1990.

Nagy, L.M.; Krystal, J.H.; Woods, S.W.; and Chamey, D.S. Clinical and medication outcome after short-term alprazolam and behavioral group treatment of panic disorder. *Arch Gen Psychiatry* 46(11):993-999, 1989.

National Institutes of Health. Treatment of panic disorder. *NZH Consens Dev Conf Consens Statement* 9(2):September 25-27, 1991.

Niaura, R.S.; Rohsenow, D.J.; Binkoff, J.A.; Monti, P.M.; Pedraza, M.; and Abrams, D.B. Relevance of cue reactivity to understanding alcohol and smoking relapse. *J Abnorm Psychol* 97(2):133-152, 1988.

Noyes, R.; Garvey, M.; and Cook, B. Follow up study of patients with panic attacks treated with tricyclic antidepressants. *J Affec Disord* 16(1-2):249-257, 1989.

Noyes, R.; Garvey, M.J.; Cook, B.; and Suelzer, M. Controlled discontinuation of benzodiazepine treatment for patients with panic disorder. *Am J Psychiatry* 148(4):517-523, 1991.

O'Brien, C.P.; Childress, A.R.; McLellan, T.; and Ehrman, R. Integrating systematic cue exposure with standard treatment in recovering drug dependent patients. *Addict Behav* 15:355-365, 1990.

O'Connell, K.A., and Martin, E.J. Highly tempting situations associated with abstinence, temporary lapse, and relapse among participants in smoking cessation programs. *J Consult Clin Psychol* 55:367-371, 1987.

Otto, M.W.; Jones, J.C.; Craske, M.G.; and Barlow, D.H. "Therapist's Manual for Panic Control Therapy for Benzodiazepine Discontinuation (PCT-BD)." Under agreement for publication. Albany, NY: Greywind Publications, 1994.

Otto, M.W.; Pollack, M.H.; and Barlow, D.H. "Stopping Anti-Anxiety Medications: A Workbook for Patients Wanting to Discontinue Benzodiazepine Treatment for Panic Disorder." Albany, NY: Greywind Publications, in press.

Otto, M.W.; Pollack, M.H.; Meltzer-Brody, S.; and Rosenbaum, J.F. Cognitive-behavioral therapy for benzodiazepine discontinuation in panic disorder patients. *Psychopharmacol Bull* 28(2):123-130, 1992.

Otto, M.W.; Pollack, M.H.; Sachs, G.S.; Reiter, S.R.; Meltzer-Brody, S.; and Rosenbaum, J.F. Discontinuation of benzodiazepine treatment: Efficacy of cognitive-behavior therapy for patients with panic disorder. *Am J Psychiatry* 150:1485-1490, 1993.

Pollack, M.H.; Otto, M.W.; Kaspi, S.P.; Hammemess, P.G.; and Rosenbaum, J.F. "Cognitive-Behavior Therapy for Treatment Refractory Panic Disorder." *J Clin Psychiatry* 55:200-205, 1994.

Pollack, M.H.; Otto, M. W.; Tesar, G.E.; Cohen, L.S.; Meltzer-Brody, S.; and Rosenbaum, J.F. Long-term outcome after acute treatment with clonazepam and alprazolam for panic disorder. *J Clin Psychopharmacol* 13:257-263, 1993.

Pollack, M.H., and Rosenbaum, J.F. Benzodiazepines in panic-related disorders. *J Anx Disord* 2:95-107, 1988.

Powell, J.; Gray, J.A.; Bradley, B.P.; Kasvikis, Y.; Strang, J.; Barratt, L.; and Marks, I. The effects of exposure to drug-related cues in detoxified opiate addicts: A theoretical review and some new data. *Addict Behav* 15:339-354, 1990.

Rickels, K.; Case, W.G.; Schweizer, E.; Garcia-Espana, F.; and Fridman, R. Benzodiazepine dependence: Management of discontinuation. *Psychopharmacol Bull* 26(1):63-68. 1990.

Rohsenow, D.J.; Childress, A.R.; Monti, P.M.; Niaura, R.S.; and Abrams, D.B. Cue reactivity in addictive behaviors: Theoretical and treatment implications. *Int J Addict* 25A:957-993, 1990-1991.

Rounsaville, B.J.; Glazer, W.; Wilber, C.H.; Weissman, M.M.; and Keber, H.D. Short-term interpersonal psychotherapy in methadone-maintained opiate addicts. *Arch Gen Psychiatry* 40:629-636, 1983.

Roy-Byrne, P.P., and Hommer, D. Benzodiazepine withdrawal: Overview and implications for the treatment of anxiety. *Am J Med* 84:1041-1052, 1988.

Sanchez-Craig, M.; Wilkinson, D.A.; and Walker, K. Theory and methods for secondary prevention of alcohol problems: A cognitive approach. In: Cox, W.M., ed. *Treatment and Prevention of Alcohol Problems: A Resource Manual.* Orlando, FL: Academic Press, 1987.

Sheehan, D.V.; Ballenger, J.; and Jacobsen, G. Treatment of endogenous anxiety with phobic, hysterical and hypochondriacal symptoms. *Arch Gen Psychiatry* 39:51-59, 1980.

Spiegel, D.A.; Bruce, T.J.; Falkin-Gregg, S.M.; and Nuzzarello, A. "Does Cognitive Behavior Therapy Assist Slow-Taper Alprazolam Discontinuation in Panic Disorder." *Am J Psychiatry* 151:876-881, 1994.

Telch, M.J.; Agras, W.S.; Taylor, C.B.; Rothe, W.T.; and Gallen, C. Combined pharmacological and behavioral treatment for agoraphobia. *Behav Res Ther* 23(3):325-335, 1985.

Telch, M.J., and Harrington, P.J. "Anxiety Sensitivity and Expectedness of Arousal in Mediating Affective Response to 35% Carbon Dioxide Inhalation." Paper presented at the 26th Annual Association for Advancement of Behavior Therapy Convention, Boston, MA, November 19-22, 1992.

Tesar, G.E.; Rosenbaum, J.F.; Pollack, M.H.; Otto, M.W.; Sachs, G.S.; Herman, J.B.; Cohen, L.S.; and Spier, S.A. Double-blind placebo-controlled comparison of clonazepam and alprazolam for panic disorder. *J Clin Psychiatry* 52(2):69-76, 1991.

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Some Methodological Comments

Kenneth I. Howard

At the first meeting of the Society for the Exploration of Psychotherapy Integration (SEPI), this author was talking to a senior psychotherapist about his experiences in trying to integrate different theoretical constructs in the actual conduct of psychotherapy. He ended the conversation by saying "I tried to be an integrationist for a year, but it gave me such a headache that I went back to being eclectic."

The contrast suggested by this poignant statement is between integration and combination. Integration requires a clear statement of theory that brings together constructs from two or more theoretical perspectives. This dependence on theory leads to hypothesis testing and an emphasis on the internal validity of research findings, usually requiring the methodology of randomized experiments. Treatment combination, on the other hand, entails optimum seeking-finding the best treatment for a specific type of patient. This task requires exploratory, applied research, and an emphasis on external validity. Each methodology requires replication of findings, but replication is even more important in exploratory studies (and in secondary or post hoc analyses).

In either case, types of patients and treatment goals must be specified in order to evaluate treatment efficacy. As Linehan has emphasized in this volume, these goals should be sequential (process goals-e.g., establishing a therapeutic alliance); specific interventions should be tailored for each goal, and there must be an operational method for assessing the integrity of the intervention and the attainment of goals.

THE CONDUCT OF EMPIRICAL INQUIRY

Each presenter has shown that the doing of science is an art-an investigator **must** interact with his or her data in order to find meaning. For example, each presenter took recourse to secondary, post hoc analyses, driven there by within-group heterogeneity, attrition, and other exigencies of actually executing a study. Some of these exigencies follow.

With the use of relatively small samples, randomization virtually never equates groups with regard to all potential confounding variables. For

example, what if researchers knew (on the basis of previous research) that there were four causally efficacious variables that were not controlled in a study? What are the odds that random assignment of 20 subjects to each of two groups would orthogonalize the two groups with regard to these four variables? Very slim indeed. This leaves researchers with the problem of determining whether the comparison groups are comparable. One approach to establishing comparability is to test statistically the differences between the groups on some potentially confounding variables; if the differences are not statistically significant, accept the null hypothesis. Elementary statistics say, however, that the null hypothesis can only be rejected; it can never be accepted on the basis of failure to find a significant difference. The fact that two groups are not significantly different does not imply that they are the same.

In any case, main effects are unlikely and are usually not very informative-i.e., there is always real within-group variance (i.e., variance not attributable to measurement error) to be explored. Moreover, the mean is an imaginary number that often does not represent any specific patient. In nearly every presentation of research findings, secondary (post hoc) data analyses were performed to examine what else was causally efficacious in the study. Post hoc analyses should be planned for and relevant data gathered on all patients regarding potential causal variables (e.g., severity). Researchers need to include these in research designs and give up the illusion that a study will go as proposed-it rarely does. It is in this sense that ***a randomized experiment often is a poorly designed quasi-experiment;*** poorly designed in the sense of not assessing a sufficiently broad range of variables.

Attrition is the tallest hurdle. Few patients completely comply with a treatment protocol; most are dropouts to some extent in the sense of missing data as well as missing treatment units (e.g., sessions). There is no way to correct for this without assuming some form of random attrition (i.e., estimating what the missing data would have been), and this is a logical counter-to-fact conditional.

REPORTING RESULTS

Statistical significance is rarely adequate for the communication of results. Effect sizes are better, but they are still difficult to translate into practical language. [Based on the Smith, Glass, and Miller (1980) meta-analyses, a colleague once asked me if I thought that I really made a .8 s.d. difference in my patients' lives!] The notion of statistical clinical

significance has gained-some adherents, but this, too, often is based on only psychometric considerations (i.e., the standard error of measurement) to determine reliable improvement. Obviously, clinical criteria (e.g., percent abstinent for a year) are the most meaningful.

In clinical research, special attention must be paid to the practical value of results. Researchers have to take a stand on a meaningful magnitude of improvement and report the percent of patients who meet this criterion. This provides the most clinically informative comparison of treatments and is easily understood by clinical practitioners-the researcher's most important research goals.

REFERENCE

Smith, M.L.; Glass, G.V.; and Miller, T.I. *The Benefits of Psychotherapy*. Baltimore, MD: Johns Hopkins Press, 1980.

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Comments

Stephen T. Higgins

Following are brief comments on the series of excellent presentations at the National Institute on Drug Abuse Technical Review Meeting on "Integrating Behavioral Therapies With Medications in the Treatment of Drug Dependence."

Dr. Carroll's presentation was consistent with this author's reading of the extant literature on treatments for cocaine dependence. The pharmacotherapies are not yet producing reliable positive results, but several psychosocial interventions look promising. Interventions with behavioral and cognitive behavioral orientations appear to be particularly promising. The relapse prevention approach that Dr. Carroll has been investigating (Carroll et al. 1991, 1994), the Community Reinforcement Approach (CRA) under investigation in this author's clinic (Higgins and Budney 1993, pp. 97-122; Higgins et al. 1991, 1993, 1994), the contingency management procedures under investigation in Dr. Stitzer's clinic (Stitzer et al. 1992), and the enhanced therapy reported by McLellan and colleagues (McLellan et al. 1993), which involved contingency management procedures, have all been efficacious in decreasing cocaine abuse in randomized, controlled trials. The consistently positive outcomes observed with the behavioral and cognitive behavioral interventions is not unique to cocaine dependence. A similar picture has emerged in treatments for problem drinking (Miller and Hester 1986, pp. 121-174) and smoking (U.S. Department of Health and Human Services 1988), and is consistent with the extensive basic science literature demonstrating a fundamental role of reinforcement and other learning factors in the genesis and maintenance of substance abuse (Goldberg and Stolerman 1986). The efficacy of behavioral interventions is great news and underscores the importance of placing comparable priority on behavioral and pharmacological initiatives in the development of treatments for drug dependence. Until recently, efforts in treatment development for cocaine dependence appeared to be disproportionately slanted in the direction of pharmacotherapies.

Dr. Hughes' presentation illustrated an important basic tenet of behavioral pharmacology: the behavioral effects of drugs are not inherent properties of the molecular structure of the compound but, instead, depend on the behavioral/environmental context in which the drugs are

administered (McKearney and Barrett 1978, pp. 1-68). Dr. Hughes' data showed in a compelling manner that behavior therapies can potentiate the efficacy of nicotine replacement therapy. Understanding the mechanisms controlling that potentiation should enhance the efficacy of smoking cessation interventions and could extend the researcher's understanding of the basic behavioral pharmacology of nicotine.

Dr. Hughes' point regarding the need to carefully specify what is meant by the term behavior therapy is an important one-one that is likely to become more important as researchers attempt to treat those who continue smoking despite the widespread social pressures to quit. By definition, such individuals have illustrated that their smoking is resistant to a variety of different behavioral interventions that are occurring in their environment. The clinical challenge is one of carefully specifying the therapeutic conditions under which their smoking will remit.

Dr. O'Farrell's work with monitored disulfiram therapy also illustrates the need to specify the conditions under which pharmacotherapies are effective. Like naltrexone, disulfiram therapy appears to be underutilized. The research of Dr. O'Farrell and colleagues (O'Farrell et al. 1992) and Azrin and colleagues (Azrin et al. 1982) illustrate that through the use of behavioral contracts and other medication compliance procedures, disulfiram can be an effective intervention in alcoholics. More research is needed on methods to effectively introduce disulfiram to patients, which is an essential but not well understood step in the successful use of this medication. It is very likely that Dr. O'Farrell's experience is like this author's. With experience, clinicians become progressively more effective in getting patients to initiate monitored disulfiram therapy. These skills could be operationalized, researched, and possibly have the potential to improve the use of disulfiram as well as other pharmacotherapies like naltrexone (Miller 1993, pp. 303-321). Such a technology is especially important to the optimal use of any pharmacotherapy in substance abusers in which the medication does not function as a positive reinforcer or eliminate adverse withdrawal signs or symptoms.

Dr. O'Malley's chapter on treating alcoholism with naltrexone is encouraging in that it offers promise of a broader array of efficacious medications for use in problem drinkers. The clinical findings parallel new and interesting basic science observations regarding possible mechanisms by which opioid systems may be involved in the neuropharmacology of ethanol (Benjamin et al. 1993). It is significant to

note the apparently high levels of compliance with naltrexone therapy in alcoholics. Certainly that differs from the experience of naltrexone therapy in opioid-dependent patients or disulfiram therapy in alcoholics. Those differences are very interesting and may offer an opportunity to improve the researchers' understanding of the factors that control medication compliance in substance abusers. Possibly part of the reason alcoholics comply with naltrexone therapy is that they can continue to drink without complete blockade of the reinforcing effects or any notable adverse effects.

With regard to the efficacy of naltrexone in decreasing drinking in alcoholics, controlled trials comparing naltrexone to disulfiram could soon be underway. Such trials would seem to provide an important context for understanding the potential contribution of naltrexone to the treatment of problem drinking. To this author's knowledge, the only study reported on that topic was a preliminary trial conducted by the Yale group examining naltrexone and disulfiram therapies in alcoholics who were also cocaine dependent (Carroll et al. 1993). In that report, naltrexone appeared much less efficacious than disulfiram in decreasing alcohol or cocaine use, both of which were decreased significantly by disulfiram therapy. Of course, any greater efficacy of disulfiram therapy in decreasing drinking in the short term might be offset by greater patient compliance with naltrexone therapy in the long term. Thus, it will be important that such trials examine the short- and long-term efficacy of these compounds and also whether or not naltrexone therapy might be acceptable to a larger proportion of alcoholics than disulfiram therapy.

With regard to Dr. Rounsaville's presentation, already mentioned was the importance of researching various methods for introducing patients to disulfiram and naltrexone and, of course, maintaining compliance with these medication regimens. The incentive studies by Meyer and colleagues (Meyer et al. 1976) and Grabowski and colleagues (Grabowski et al. 1979), in this author's opinion, merit followup studies. There are many ways to reinforce behavior. If paying a couple of dollars effectively maintains naltrexone compliance, it is likely that other reinforcers could work as well. Researchers must be careful not to hastily dismiss studies on incentives of the sort that Meyer and colleagues and Grabowski and colleagues investigated. They represent important initial steps toward addressing the important reinforcement issues involved in naltrexone therapy.

Dr. O'Brien's presentation provided a compelling demonstration of the benefits of integrating pharmacological and psychosocial therapies in the treatment of drug dependence. The important advances those studies represent really need no additional comment here. However, one observation reported by Dr. O'Brien to encourage additional research should be mentioned. Dr. O'Brien outlined the clinical improvements gained by providing supportive expressive and cognitive behavioral psychotherapy to depressed methadone-maintenance patients (Woody et al. 1991, pp. 152-166). Improvements were evident even in those depressed patients who also had Antisocial Personality Disorder (APD), but not those who had APD without depression. This latter group did not derive any discernible benefits from these psychotherapeutic interventions. Whether such APD methadone-maintenance patients might have benefited from an alternative intervention, to this author's knowledge, was not investigated, but it illustrates an important direction for future drug abuse research. In alcoholics, for example, patients scoring high on measures of sociopathy and global psychopathology have significantly better outcomes across a 2-year followup period if they received coping skills training rather than interactional therapy (Cooney et al. 1991). More research is needed examining specific psychosocial and pharmacological interventions for specific co-morbid psychiatric disorders in specific types of drug abusers. By carefully specifying their interventions, the other psychiatric disorders targeted, and the particular drug abuse disorders involved, researchers will be in a position to discern basic functional relationships among these complicated co-morbid disorders. Such efforts would likely facilitate both more effective clinical practices, including patient-treatment matching, and improve researchers' basic understanding of how these co-morbid disorders are related, which at this time still seems somewhat muddled.

One area not specifically touched on in Dr. O'Brien's presentation that merits more research is how to make greater therapeutic use of the reinforcing effects of methadone. Methadone can be a potent reinforcer in the opioid-dependent population (Bickel et al. 1986). Unfortunately, little explicit therapeutic use is made of that function. Granted, researchers inadvertently reinforce clinic attendance by requiring that patients ingest their medication under staff observation. Typically, staff does so well on that front that loitering becomes a problem. What is needed is more research directed at using methadone to reinforce other types of behavior important to treatment process (e.g., abstinence from illicit drugs and involvement in educational and other prosocial behaviors).

A trial this author conducted with Dr. Stitzer and colleagues illustrates how methadone's reinforcing effects can support abstinence from illicit opiates (Higgins et al. 1986). Opiate-dependent patients were randomized to three treatment groups during a 90-day outpatient detoxification. In one treatment group, patients could receive methadone dose supplements contingent on submitting urine specimens that were opiate-negative in urinalysis testing (contingent group); in a second group, they could obtain the same dose supplements independent of urinalysis results (noncontingent group); in a third group, they were ineligible for dose supplements (control group). The contingent and noncontingent groups had significantly lower percentages of opiate-positive urinalysis results than the control group, demonstrating the efficacy of the extra medication in suppressing illicit opiate use, probably through cross-tolerance and satiation (figure 1). Importantly, the contingent group had significantly lower percentages of opiate-positive urinalysis results than the noncontingent group, demonstrating the additional efficacy gained by utilizing methadone's reinforcing effects to directly strengthen abstinence from illicit drug use. As was noted above, methadone can be a powerful reinforcer in the opiate-dependent population, and researchers should carefully consider how that feature might be more effectively incorporated into the treatment process.

Regarding Dr. Linehan's presentation, this author would like to expound on a point she made regarding extra efforts to retain patients in treatment. This author is a proponent of what amounts to an outreach approach to treatment of ambulatory substance abuse patients. In this author's CRA treatment for cocaine dependence, for example, staff members telephone patients, mail them letters, and have street workers attempt to locate patients if they fail to show up for a scheduled therapy session. (CRA does not permit patients to easily discontinue treatment.) Considering the well-known associations between treatment retention and outcome, this approach makes sense. However, experimental data are needed to appropriately assess whether such outreach procedures are effective in decreasing drug use or improving other outcomes. Considering the ever-growing relationships between substance abuse and many of society's health and social problems, identifying effective strategies to promote treatment retention should be an important research priority.

Dr. Otto's presentation underscores the function that behavioral therapies can serve even with disorders for which effective pharmacotherapies exist; an observation that is consistent with the recent study by McLellan and colleagues (1993) demonstrating the benefits of combining enhanced

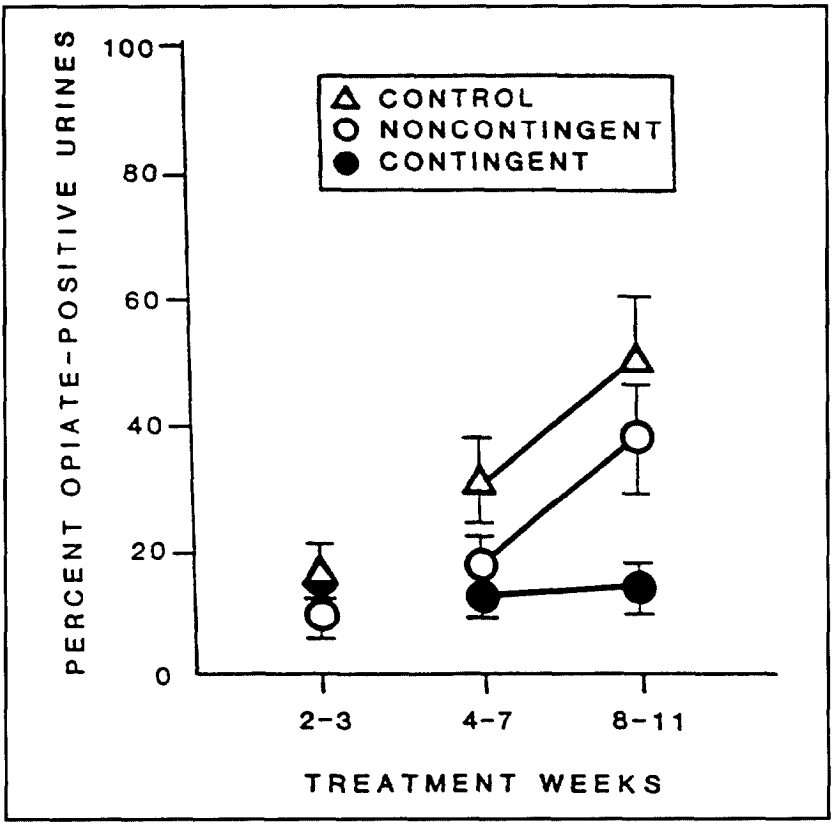

FIGURE 1. *Percent opiate-positive urinalysis results as a function of consecutive treatment weeks. Results obtained during a dose-stabilization period (weeks 2-3) are presented as a 2-week block and results during the intervention period (weeks 4-12) are presented in two I-week blocks. The contingent group is represented by closed circles, the noncontingent group by open circles, and the control group by triangles; brackets represent +/- 1 SEM.*

SOURCE: Higgins et al. (1986).

psychosocial services with methadone therapy. Effective pharmacotherapies do not obviate the need for effective behavioral interventions.

Two other points illustrated in Dr. Otto's presentation are the importance of a theoretically cohesive model of the target disorder and the

appropriate utilization of laboratory studies in efforts to understand and treat the problem. In this author's opinion, substance abuse research often is conducted outside of any obvious theoretical model, and often it is difficult to discern much, if any, interaction between laboratory and treatment research efforts. This is probably more the case regarding behavioral than pharmacological factors, but improvements could be made in both areas. Behavioral pharmacology has much to offer substance abuse researchers in terms of a cohesive theoretical model and rich basic science literature on behavioral and pharmacological factors involved in the genesis and maintenance of substance abuse (Schuster 1986, pp. 357-385).

Regarding Dr. Weiss's presentation, it was noted earlier how important it is that researchers experimentally assess for functional relationships between specific types of co-morbid psychiatric disorders and substance abuse. Doing so is likely to advance researchers' basic understanding of the disorders involved as well as their ability to treat them. When considering the high prevalence of substance abuse in populations with other psychiatric disorders, it seems that researchers may be too apt to hypothesize self-medication and other accounts that are unique to these populations. A reasonable alternative approach is to examine whether some of the more generic factors that contribute to substance abuse in the general population might also be present in psychiatric patients. The high levels of unemployment, economic deprivation, familial dysfunction, and social isolation common in psychiatrically disturbed individuals, for example, might increase risk both for drug abuse and other psychiatric problems. Said another way, these populations may be deprived of access to alternative, prosocial reinforcers that can effectively compete with the reinforcing effects of abused drugs (Schuster 1986, pp. 357-385). Examining how such factors influence this apparent greater vulnerability to substance abuse in psychiatric populations might result in a more parsimonious account of their drug-using behavior.

REFERENCES

Azrin, N.H.; Sisson, R.W.; Meyers, R.; and Godley, M. Alcoholism treatment by disulfiram and community reinforcement therapy. *J Behav Ther Exp Psychiatry* 13:105-112, 1982.

Benjamin, D.; Grant, E.R.; and Pohorecky, L.A. Naltrexone reverses ethanol-induced dopamine release in the nucleus accumbens in awake, freely moving rats. *Brain Res* 621:137-140, 1993.

Bickel, WK.; Higgins, S.T.; and Stitzer, M.L. Choice of blind methadone dose increases by methadone maintenance patients. *Drug Alcohol Depend* 18:165-171, 1986.

Carroll, K.M.; Rounsaville, B.J.; and Gawin, F.H. A comparative trial of psychotherapies for ambulatory cocaine abusers: Relapse prevention and interpersonal psychotherapy. *Am J Drug Alcohol Abuse* 17:229-247, 1991.

Carroll, K.M.; Rounsaville, B.J.; Gordon, L.T.; Nich, C.; Jatlow, P.; Bisighini, R.M.; and Gawin, F.H. Psychotherapy and pharmacotherapy for ambulatory cocaine abusers. *Arch Psychiatry* 51:177-187, 1994.

Carroll, K.; Ziedonis, D.; O'Malley, S.; McCance-Katz, E.; Gordon, L.; and Rounsaville, B. Pharmacologic interventions for alcohol- and cocaine-abusing individuals. *Am J Addict* 2:77-79, 1993.

Cooney, N.L.; Kadden, R.M.; Litt, M.D.; and Getter, H. Matching alcoholics to coping skills or interactional therapies: Two-year follow-up results. *J Consult Clin Psychol* 59:598-601, 1991.

Goldberg, S.R., and Stolerman, I.P. *Behavioral Analysis of Drug Dependence.* Orlando, FL: Academic Press, Inc., 1986.

Grabowski, J.; O'Brien, C.P.; Greenstein, R.; and Temes, J. Effects of contingent payment on compliance with a naltrexone regimen. *Am J Drug Alcohol Abuse* 6:355-365, 1979.

Higgins, S.T., and Budney, A.J. Treatment of cocaine dependence through the principles of behavior analysis and behavioral pharmacology. In: Onken, L.S.; Blaine, J.D.; and Boren, J.J., eds. National Institute on Drug Abuse Research Monograph 137. *Behavioral Treatments for Drug Abuse and Dependence.* NIH Pub. No. (ADM)93-3684. Washington, DC: Supt. of Docs., U.S. Govt. Print. Off., 1993.

Higgins, S.T.; Budney, A.J.; Bickel, W.K.; Foerg, F.E.; Donham, R.; and Badger, G.J. Incentives improve outcome in outpatient behavioral treatment of cocaine dependence. *Arch Gen Psychiatry* 51:568-576, 1994.

Higgins, S.T.; Budney, A.J.; Bickel, W.K.; Hughes, J.R.; Foerg, F.; and Badger, G. Achieving cocaine abstinence with a behavioral approach. *Am J Psychiatry* 150:763-769, 1993.

Higgins, ST.; Delaney, D.D.; Budney, A.J.; Bickel, W.K.; Hughes, J.R.; Foerg, F.; and Fenwick, J.W. A behavioral approach to achieving initial cocaine abstinence. *Am J Psychiatry* 148:1218-1224, 1991.

Higgins, S.T.; Stitzer, M.L.; Bigelow, G.E.; and Liebson, I.A. Contingent methadone delivery: Effects on illicit opiate use. *Drug Alcohol Abuse* 17:311-322, 1986.

McKearney, J.W., and Barrett, J.E. Schedule-controlled behavior and the effects of drugs. In: Blackman, D.E., and Sanger, D.J., eds. *Contemporary Research in Behavioral Pharmacology*. New York: Plenum Press, 1978.

McLellan, A.T.; Amdt, 1.0.; Metzger, D.S.; Woody, G.E.; and O'Brien, C.P. The effects of psychosocial services in substance abuse treatment. *JAMA* 269:1953-1959, 1993.

Meyer, R.; Randall, M.; Barrington, B.A.; Mirin, S.; and Greenberg, I. Limitations of an extinction approach to narcotic antagonist treatment. In: Julius, D., and Renault, P., eds. National Institute on Drug Abuse Research Monograph 9. *Narcotic Antagonists: Naltrexone.* DHEW Pub. No. (ADM)76-0000. Washington, DC: Supt. of Docs., U.S. Govt. Print. Off., 1976.

Miller, W.R. Behavioral treatments for drug problems: Where do we go from here? In: Onken, L.S.; Blaine, J.D.; and Boren, J.J., eds. *Behavioral Treatments for Drug Abuse and Dependence.* National Institute on Drug Abuse Research Monograph 137. NIH Pub. No. (ADM)93-3684. Supt. of Docs., U.S. Govt. Print. Off., 1993.

Miller, W.R., and Hester, R.K. The effectiveness of alcoholism treatment methods: What research reveals. In: Miller, W.R., and Heather, N., eds. *Treating Addictive Behaviors: Processes of Change.* New York: Plenum Press, 1986.

O'Farrell, T.J.; Cutter, H.S.G.; Choquette, K.A.; Floyd, F.J.; and Baylog, R.D. Behavioral marital therapy for male alcoholics: Marital and drinking adjustment during the two years after treatment. *Behav Ther* 23:529-549, 1992.

Schuster, C.R. Implications of laboratory research for the treatment of drug dependence. In: Goldberg, S.R., and Stolerman, I.P., eds. *Behavioral Analysis of Drug Dependence.* Orlando, FL: Academic Press, Inc., 1986.

Stitzer, M.L.; Iguchi, M.Y.; and Felch, L.J. Contingent take-home incentive: Effects on drug use of methadone maintenance patients. *J Consult Clin Psychol* 60:927-934, 1992.

U.S. Department of Health and Human Services. *The Health Consequences of Smoking: Nicotine Addiction, A Report of the Surgeon General.* DHHS Pub. No. (CDC)88-8406. Washington, DC: Supt. of DOCS., U.S. Govt. Print. Off., 1988.

Woody, G.E.; McLellan, A.T.; O'Brien, C.P.; and Luborsky, L. Addressing psychiatric comorbidity. In: Pickens, R.W.; Leukefeld, C.G.; and Schuster, C.R., eds. *Improving Drug Abuse Treatment.* National Institute on Drug Abuse Research Monograph 106. DHHS Pub. No. (ADM)91-1754. Supt. of Docs., U.S. Govt. Print. Off., 1991.

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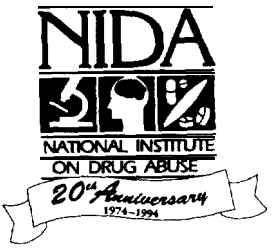

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