Treatment of Depression in Drug-Dependent Patients: Effects on Mood and Drug Use

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INTRODUCTION

Symptoms of depression and anxiety are common in patients with substance use disorders (Meyer 1986; Schuckit 1986). In the general population, mood and anxiety disorders convey increased risk for substance use disorders (Regier et al. 1990). Further, mood-disordered substance abusers have poor prognoses (Rounsaville et al. 1982*b*, 1986*b*, 1987; Weissman et al. 1976; Kosten et al. 1986; LaPorte et al. 1981; Loosen et al. 1990; Carroll et al. 1993). Thus, evaluation and appropriate management of affective disorders should be a useful treatment adjunct with the potential of improving outcome of substance abuse. Nevertheless, controversy continues to surround this clinical problem, and approaches vary widely among clinicians.

Further, the problem of the depressed substance abuser raises important theoretical questions about the etiology and pathogenesis of substance abuse disorders. Mood syndromes observed in substance-dependent patients often resolve soon after abstinence or the initiation of specific treatment such as methadone (Weddington et al. 1990; Rounsaville et al. 1986*a*; Schuckit 1986; Willis and Osbourne 1978; DeLeon et al. 1973), suggesting a "substance-induced" (American Psychiatric Association 1994) syndrome (i.e., toxicity or withdrawal) or transient adjustment reactions. However, in 10 percent or more of these patients in various clinical samples, depression persists (Nakamura et al. 1983; Johnson and Perry 1986; Rounsaville et al. 1986*a*; Croughan et al. 1981). These persons may have a mood disorder that is independent of substance abuse. Because both substance abuse and mood disorders are common in the general population, it can be expected that some individuals will have both disorders by chance alone.

Another possibility is that a subgroup has mood disorders that contribute to the etiology of substance abuse. In fact, a self-medication hypothesis has been advanced (Khantzian 1985; Quitkin et al. 1972) suggesting that some individuals use drugs because they provide temporary relief from symptoms of depression or anxiety.

Depression or anxiety may be the sole etiology or one of several causal factors, including other genetic and environmental vulnerabilities, in substance abuse. Also, depression or anxiety may alter the course of substance abuse. For example, depression is a frequent internal cue triggering drug craving (Marlatt and Gordon 1985; Daley and Marlatt 1992). Thus, an initially independent depressive disorder, through classical conditioning (Childress et al. 1994), may become linked to relapse and perpetuate substance abuse.

The evidence that the self-medication hypothesis plays a contributory role in some substance abuse stems mainly from clinical observations (Khantzian 1985; Marlatt and Gordon 1985) and epidemiologic data (Regier et al. 1990). However, the strongest test of the hypothesis would be one that directly addresses its clinical utility, namely, whether treatment of depression or anxiety alters the course and outcome of substance abuse. Specifically, if depression contributes to the etiology of substance abuse, then antidepressant treatment should improve substance abuse outcome. Relatively few studies of this type have been undertaken, and most have methodologic problems. This chapter reviews this literature as well as the authors' recent studies, drawing tentative conclusions and developing suggestions for future research.

The present approach to evaluating the literature is summarized in table 1 (Nunes et al., in press). Studies evaluated are those in which patients with substance use disorders who also display evidence of depression receive antidepressant medication treatment. If there is no medication-placebo difference in both mood and substance use outcome (right column, table 1), and particularly if the placebo-mood response is high, a transient substance-induced mood syndrome or adjustment reaction is suggested. If mood improves on medication compared to placebo, but substance use does not (middle column, table 1), it suggests a true mood disorder that is independent of substance abuse. Finally, if both mood and substance use improve on medication (left column, table 1), it suggests that the depression contributes to the etiology of substance abuse, as in self-medication.

Antidepressant Treatment in Alcoholism

In the 1960's and 1970's, nine placebo-controlled studies of antidepressant medications (mainly tricyclics) (TCAs) in alcoholic

TABLE 1. *Predicted outcome of antidepressant treatment across mood disorder/substance abuse relationships.*

	Depression contributes to substance abuse: "self-medication"	Depression and substance abuse are independent	Depression is substance-induced
Mood improves (vs. placebo)	Yes	Yes	No (high placebo resonse)
Drug use improves (vs. placebo)	Yes	No	No

SOURCE: Adapted from Nunes et al. 1994.

patients were reported. These studies have been reviewed extensively by Ciraulo and Jaffe (1981) and by Liskow and Goodwin (1987). No study demonstrated superiority of TCAs except for some short-lived effects, probably attributable to amelioration of withdrawal symptoms. However, both research pairs concluded that the studies were seriously flawed and that further study of antidepressant medication treatment of depressed alcoholics was needed. Both the doses of TCAs and the trial lengths (mostly 3 weeks or less) were inadequate. Outcome measures were narrowly focused on either depression or drinking behavior, but not both. Methods of diagnosing affective disorder were either unspecified or based on cross-sectional scales, which are not adequate measures of primary affective disease in the setting of alcoholism (Keeler et al. 1979).

One promising pilot study did demonstrate successful open treatment with imipramine of a small series of alcohol and sedative abusers with panic disorder (Quitkin et al. 1972). This study had the advantage of a carefully diagnosed, homogeneous sample, but required replication in larger controlled trials.

In a first replication attempt, Nunes and colleagues (1993) conducted an open-label trial of imipramine followed by double-blind, placebo-controlled discontinuation for responders. Subjects were outpatients who currently met criteria for *Diagnostic and Statistical Manual of Mental Disorders*, 3d ed. revised (DSM-III-R) (American Psychiatric Association 1987) alcohol abuse or dependence and also had DSM-

III-R major depression or dysthymia. Experienced research psychiatrists interviewed and diagnosed the patients. Depressive syndromes were either chronologically primary, antedating the onset of alcohol abuse on a lifetime basis, had persisted during past abstinent periods, or were chronic.

Eighty-five patients met inclusion criteria and entered the trial, and 60 completed the minimum adequate trial of 6 weeks of imipramine. The mean dose of imipramine was 263±77 mg/day and the mean blood level was 368±264 nanograms per milliliter (ng/mL). In addition to weekly visits with a treating psychiatrist, each patient received one weekly session of alcoholism counseling, and all patients were encouraged to attend Alcoholics Anonymous. Of the 60 completers, 27 (45 percent) were rated as "responders" to open imipramine after the initial 12 weeks with a substantial improvement in both mood Clinical Global Impression (CGI) change score of 2, "much improved," or 1, "very much improved," and drinking behavior. A rating of substantial improvement in drinking required either abstinence (18 cases, 30 percent) or a substantial reduction in quantity consumed and an absence of functional impairment. Another three patients responded after increases in imipramine dosage, and five more responded after brief courses of disulfiram, so that a total of 35 (58 percent) were ultimately called responders.

Twenty-three of the responders entered and completed the 6-month, double-blind discontinuation phase in which they were randomized either to remain on imipramine or taper off imipramine onto placebo. The principal endpoint was relapse during the 6-month followup period, defined as loss of either mood response or drinking response or both. The relapse rate was lower on imipramine (31 percent, 4/13) than on placebo (70 percent, 7/10), a difference that approached statistical significance (Fisher's exact $p = 0.09$, two-tailed). Most relapses involved near-simultaneous return of both depression and drinking.

This study differed from previous research by providing a medication trial of adequate dosage and duration, and by selecting depression via syndromal criteria rather than cross-sectional symptoms. The results suggest that antidepressant medication treatment is useful in depressed outpatient alcoholics, both in treating depression and in inducing remission of drinking and preventing relapse. The findings provide preliminarily support for the hypothesis that depression plays some role in the etiology of drinking in a selected subgroup.

Replication is clearly needed in larger controlled trials, along with further work on developing criteria for selecting medication-responsive depressed alcoholics. The majority of patients selected for this trial had depression that was chronologically primary, because the investigators felt that this history would characterize self-medicators. Interestingly, Mason and Kocsis (1991) recently completed a methologically sound, placebo-controlled trial of desipramine in alcoholics who all had depression that was chronologically secondary, but had persisted during inpatient detoxification. Their results also suggested that desipramine was useful in treating both depression and drinking (Mason and Kocsis 1991). This suggests that the primary-secondary distinction may be of limited utility as a selection criterion, since both primary and secondary depressions appear to respond to medication. Persistence of depression after inpatient detoxification may be more useful, although in practice it is not always possible to arrange hospitalization.

LITHIUM TREATMENT OF ALCOHOLISM

Lithium has actually been extensively studied as a treatment for alcoholism. The older literature contains four double-blind, placebo-controlled studies (Fawcett et al. 1984, 1987; Pond et al. 1981; Merry et al. 1976; Kline et al. 1974) in which patients were not selected for depression, but outcome was compared in depressed and nondepressed subgroups. A principal hypothesis of the studies was that lithium would have a direct effect on drinking behavior independent of its mood- stabilizing effects. Depression was assessed with cross-sectional scales rather than by clinical history and syndromal diagnosis. In three of the studies (Fawcett et al. 1987; Merry et al. 1976; Kline et al. 1974), lithium-treated patients showed a significant reduction in alcohol consumption compared to controls. In the fourth study this effect held only for the depressed subgroup (Merry et al. 1976). However, none of the studies detected a significant reduction of depression symptoms in the lithium-treated groups compared to placebo groups. Depression scores tended to be reduced at followup in all subjects, suggesting a high placebo response rate. On balance, these early findings suggested that lithium might have a salutary effect on alcoholism that might be unrelated to its mood-altering effect. Another possibility is that lithium might modulate alcohol intake via serotonergic mechanisms, reminiscent of preclinical studies suggesting that serotonin uptake inhibitors may reduce self-administration of alcohol (Gorelick 1989; Naranjo et al. 1990) and cocaine (Carroll et al. 1990; Kleven and Woolverton

1993). The suggestion is instructive because it highlights the possibility that an antidepressant medication might directly influence the pathophysiology of addiction quite apart from any effects on mood.

Subsequently, a large and well-designed multicenter trial failed to detect any effect of lithium on drinking behavior, even in the subsample with syndromal major depression (Dorus et al. 1989). This failure to replicate is consistent with several possibilities, including that of a very modest efficacy of lithium. However, the findings are inconclusive on the notion of a medication-responsive depressed subgroup. The data indicate that a lithium-responsive depressed subgroup seems unlikely, but lithium is at best a modestly effective antidepressant.

Antidepressant Treatment in Cocaine Abuse

In an approach reminiscent of studies on lithium in alcoholism, a number of placebo-controlled trials of desipramine (Gawin et al. 1989; Giannini and Billett 1987; Weddington et al. 1991; Arndt et al. 1992; Kosten et al. 1992; Carroll et al. 1994) have been conducted to test whether desipra-mine has a direct effect on cocaine use behavior, independent of its antidepressant effects. This hypothesis stems in part from preclinical studies showing that tricyclic antidepressants reverse stimulant-induced changes in intracranial self-stimulation (Markou et al. 1992). Depression was not an inclusion criterion for these studies.

In the first large trial in this series, Gawin and colleagues (1989) showed a robust, favorable effect of desipramine on cocaine use and craving. The effect was not diminished when the small subgroup with major depression was removed from the analysis, suggesting that it was indeed independent of any antidepressant effects. Large placebo-controlled trials have subsequently failed to replicate the robust effect, although several suggested that a desipramine effect may occur early in treatment (Kosten et al. 1992, Carroll et al. 1994) or in the mildly ill subgroup (Carroll et al. 1994). Of interest to this review, a secondary analysis of one of the studies (Ziedonis and Kosten 1991) showed a favorable effect of desipramine on cocaine use in the subsample with depression at baseline. Also several studies demonstrated a desipramine effect on mood (Giannini and Billett 1987) or psychological symptoms (Arndt et al. 1992). Similarly, preliminary analysis of a study by the authors of imipramine for

cocaine abuse suggests that tricyclic antidepressants may reduce cocaine use in the subsample with depression (Nunes et al. 1995).

Fluoxetine also showed some promise for treatment of cocaine abuse in initial open (Batki et al. 1991) and placebo-controlled trials (Batki et al. 1993), although subsequent placebo-controlled trials (Covi et al. 1995, Grabowsky et al. 1995) have failed to replicate these findings. Once again, depression was not an inclusion criterion. To date, no study of either desipramine or fluoxetine has focused exclusively on depressed cocaine abusers.

Antidepressant Treatment in Opiate Addiction

During the 1970's and early 1980's, six randomized, double-blind, placebo-controlled trials of tricyclic antidepressants in methadone-maintained or detoxifying opiate addicts were reported (Kleber et al. 1993; Woody et al. 1982, 1975; Goldstein et al. 1992; Titievsky et al. 1982; Batki et al. 1987). These studies, summarized in table 2, were stronger methodologically than the older literature on TCAs in alcoholism, and in contrast to the studies on antidepressants for cocaine abuse, they all selected subjects with evidence of current depression. All but one (Titievsky et al. 1982) measured both mood and drug use outcomes. Sample sizes were mainly small ($N < 50$). Trial lengths were usually 4 weeks, which is adequate, although minimally so (Quitkin et al. 1984). Doses of tricyclics were low (Quitkin 1985). However, methadone slows the metabolism of TCAs (Kosten et al. 1990), so that adequate blood levels may actually have been achieved, even though blood level monitoring was not employed.

As shown in table 2, four of five studies employing doxepin report superiority to placebo on measures of depression (Goldstein et al. 1982; Woody et al. 1975; Titievsky et al. 1982; Batki et al. 1987). Three found medication superior to placebo on at least a few self-report drug abuse outcome measures (Woody et al. 1982, 1975; Batki et al. 1987). However, another three either lacked drug abuse outcome measures (Titievsky et al. 1982) or detected no medication versus placebo differences on drug abuse measures (Kleber et al. 1983; Goldstein et al. 1982). No studies found doxepin effects on urine toxicology. Thus, the evidence for a doxepin effect on drug abuse is equivocal.

TABLE 2. *Double-blind, placebo-controlled trials of tricyclic antidepressants in methadone patients.*

Author, year	Sample size	Medication, dose range, duration	Depression inclusion criterion	Depression outcome drug > placebo	Drug use outcome drug > placebo
Woody et al. 1975	35	doxepin 150 mg/day, 4 weeks	clinical psychiatric interview	+	+/-
Titievsky et al. 1982	46	doxepin 200 mg/day, 4 weeks	Ham-D > 18	+	not reported
Woody et al. 1982	30	doxepin vs desipramine 4 weeks	unspecified	+/- P*	+/-
Goldstein et al. 1982	44	doxepin 100 mg/day, 12 months	unspecified	+/- P*	-
Kleber et al. 1983	46	imipramine 150-225 mg/day, 8 weeks	clinical interview (DSM-II) Raskin > 7	- P*	-
Batki et al. 1987	81	doxepin 12 weeks	DSM-III major depression	+/-	+/-

KEY: * P = High placebo response rate observed in depression outcome measures.

SOURCE: Adapted from Nunes et al. 1994.

In a three-group design, Woody and associates (1982) found trends suggesting that desipramine was no better than placebo and inferior to doxepin, although the sample size (N = 10 per cell) was too small for a conclusive analysis. Another study found that imipramine had no effect on either depression or drug abuse (Kleber et al. 1983). Because imipramine and desipramine are relatively nonsedating TCAs, the suggestion is that doxepin may work in this population through nonspecific sedative effects (Kleber et al. 1983; Woody et al. 1982).

In summary, several of these studies demonstrated clear-cut antidepressant effects of TCAs in opiate addicts, but none demonstrated clear effects on drug abuse outcome. These findings suggest that depression can be identified and treated in methadone maintained opiate addicts, but is, at least in many cases, an independent disorder that does not contribute to the etiology of addiction.

It is also possible that methodologic shortcomings, including inadequate doses and trial lengths, contributed to a failure to demonstrate decreased drug use. Further, the placebo groups improved substantially in three of the trials (Kleber et al. 1983; Woody et al. 1982; Goldstein et al. 1982). A high placebo response rate makes detection of medication effects difficult, suggesting that the samples were heterogeneous and primarily evidenced transient dysphorias that resolved spontaneously. All studies studied depressed patients using cross-sectional symptom scales rather than clinical history and syndromal diagnosis. As noted, depression in opiate addicts is often transient (Rounsaville 1986*a*; DeLeon et al. 1973), which suggests that antidepressant treatment of homogeneous samples with primary or chronic affective disease would yield more robust effects on mood and drug use.

With the benefit of hindsight on earlier design shortcomings, the authors and colleagues have sought to test the effectiveness of a standard antidepressant, imipramine, for the treatment of depression and drug abuse in methadone patients. Designs included minimum adequate trial lengths of at least 6 weeks, dosages of 150 to 300 mg/day, and selection of depressed subjects through diagnostic interviews by experienced clinicians who applied stringent criteria for current and lifetime DSM-III-R depressive syndromes.

Pilot Trial

The initial study was an open-label pilot trial of imipramine in a consecutive series of depressed methadone patients (Nunes et al. 1991) at a university-affiliated, community-based methadone clinic (site 1). Depression was diagnosed only if the patient met criteria for current DSM-III-R major depression or dysthymia that was either primary, had persisted during a past abstinence, or was at least of 6 months' duration in the current episode. Diagnosis was made through clinical history by experienced research psychiatrists. Twenty-four patients (10 men, 14 women) entered and 17 (7 men, 10 women) completed a minimum adequate trial of at least 6 weeks of imipramine at doses ranging from 100 to 300 mg/day (median: 250 mg/day). Of the 17 completers, 16 were using illicit drugs at baseline, 9 of 17 intravenously, and one was abstinent but experiencing strong drug cravings. Baseline Hamilton Depression (HAM-D) Scale scores ranged from moderate to severe, with a mean of 17$\pm$4. Nine patients (53 percent) were judged "responders," with marked reductions in both depression (mean posttreatment HAM-D 2$\pm$1) and illicit drug use. All patients gave weekly urines. For each patient, the percentage of urines positive for any drug, using a mirror image historical control (i.e., 6 months prior to initiation of the imipramine trial), was compared to the proportion of positive urines in a followup period of up to 11 months during which patients were maintained on imipramine. Among responders the percentage of positive urines was 54$\pm$26 at pretreatment, which dropped to 15$\pm$17 during treatment.

The nine responders in the open trial were offered continuing psychiatric treatment at the methadone clinic. Chart review of their treatment course over 4 years of followup (Nunes et al., in press) showed that depression remained improved during imipramine treatment, but relapses often occurred during attempts to taper the medication. This finding suggests that imipramine exerted a continuing antidepressant effect, although drug use recurred intermittently for several patients despite ongoing imipramine treatment, and suggests a less robust effect of the antidepressant on drug abuse.

Double-Blind, Placebo-Controlled Trial

Because the uncontrolled trial suggested that antidepressant treatment had a substantial effect on both mood and drug use in carefully selected, depressed methadone patients, the authors conducted a larger, placebo- controlled imipramine trial. Following is a

preliminary analysis of outcome for the first 80 patients to complete the study.

Sample and Methods. The design was a prospective, parallel groups, randomized, placebo-controlled trial of imipramine in methadone patients with current depression who met lifetime historical criteria similar to those described for the open-label trial. Because of the high placebo response rates experienced in other trials, patients were required to have been in methadone treatment for at least 1 month preceding study onset in order to be included, which was a further effort to exclude transient mood syndromes. The trial was conducted at the same site as the open-label trial, as well as at a second university-affiliated, community-based methadone clinic.

Global Outcome. The primary outcome measure, defined a priori, was a dichotomous response criterion requiring both a rating of at least much improved on the Clinician's Global Impression scale score for depression and at least a 75 percent reduction in self-reported drug use or of abstinence. Twenty-four of 40 (60 percent) of completers on imipramine were responders, compared to 3 of 40 (8 percent) on placebo ($0^2 = 24.3$, 1 df, $p < 0.0001$). The imipramine-placebo difference was equally robust among men, women, whites, and minorities and was similarly unaffected by clinic site or type of depression (major versus nonmajor depression, or primary versus nonprimary depression). Thus, imipramine continued to be effective, and low placebo response rate suggests that the diagnostic approach succeeded in excluded patients with transient, self-limited mood disturbances.

Continuous Outcome Measures. Preliminary analysis of continuous outcome measures reveals a mixed picture. There is a robust difference between imipramine (7.3 ± 6.6) and placebo (13.5 ± 6.3) on the post- treatment HAM-D Scale total score (effect size = 0.96) ($F = 23.3$, 75 df, $p < 0.001$). For self-reported days of use per week of each patient's most frequently abused drug, the difference between imipramine (1.6 ± 2.1) and placebo (3.3 ± 3.2) (effect size = 0.64), ($F = 5.38$, 76 df, $p < 0.03$), is less robust, although still significant. F tests reported are for main effect of medication, in an analysis of covariance (ANCOVA) with the baseline level of the dependent measure entered as a covariate. For each patient, the proportion of urines negative for all drugs (by EMIT assay) during the last 4 weeks of the study was calculated and treated as a continuous measure. There was no difference between imipramine (0.47 ± 0.41) and placebo (0.44 ± 0.41) in the proportion of drug-negative urines.

This preliminary analysis suggests that imipramine exerts a strong antidepressant effect in carefully selected methadone patients, but that its effect on illicit drug use is less robust, being manifest in self-report, but not in the urine-based measure. Replication is indicated with quantitative urinalysis, which might provide an objective measure of reduced drug use short of abstinence.

CONCLUSIONS

This chapter reviewed both the literature and the authors' recent studies bearing on the hypothesis that depression can be treated in patients with substance use disorders and that such treatment will improve the outcome of substance abuse. The literature actually covers a large number of placebo-controlled trials in which various antidepressant medications were tested as treatments in clinical populations with substance use disorders. These include studies of several antidepressants and lithium in alcoholic samples, of antidepressants in samples with cocaine abuse, as well as samples with opiate dependence.

As a whole, the literature is inconclusive on the question of whether treatment of depression is effective in such populations. Many of the studies selected depressed patients on the basis of cross-sectional mood scales rather than clinical history and syndromal diagnosis, which may have resulted in samples replete with transient, substance-induced mood syndromes or adjustment reactions to stress rather than true mood disorders. The result is high placebo response rates and little or no medication effect. Other studies, including those of cocaine abusers, were not designed to treat depression, but to test whether the medication had any direct effect on drug use behavior.

The authors and colleagues, seeking to fill the gap in the literature, are conducting a series of studies in substance abusers with depression diagnosed by clinical interview, using criteria designed to select patients with primary or chronic depression. Pilot studies in depressed outpatient alcoholics and in depressed methadone maintenance patients, as well as preliminary analysis of a large trial in methadone patients, suggest that depression can be identified in substance abusers and that it responds robustly to standard antidepressant medication treatment. There is also evidence of a beneficial effect on substance use itself, although this appears to be less robust and further study is needed to determine its true extent.

These findings have theoretical implications for the relationship between substance use disorders and depression (see table 1), suggesting that the disorders are at least in part independent. Depression can be identified and treated, and substance use may be reduced, but in most cases it does not vanish as one would predict were a patient taking drugs purely to self-medicate. Instead, depression is probably only one of several factors that contribute to the onset or maintenance of an addiction. It is also possible that mood disorders are responsible for initiation of drug use, but that the drug use itself is so rewarding that it takes on a life of its own.

In terms of clinical implications, the conclusion that pure self-medication is rare does not diminish the importance of identifying and treating depression as part of a comprehensive plan of addiction treatment. Even if depression and addiction are entirely independent disorders, depression carries its own associated morbidity and mortality (Murphy et al. 1992). There is ample evidence that psychopathology is associated with poor prognosis for substance abuse. The effect of ameliorating these symptoms on prognosis of drug abuse requires further study.

Future Directions

These findings suggest several future directions for research. There are still relatively few well-designed studies of the treatment of comorbid psychiatric disorders in substance-dependent patients. The older studies, as noted, tended to have methodologic limitations. Recent studies on treatment of depression (Mason and Kocsis 1991; Nunes et al. 1993), as well as a recent series on buspirone in anxious alcoholics (Malcolm et al. 1992; Tollefson et al. 1990; Kranzler et al. 1994), suggest that the strategy of identifying and treating psychiatric comorbidity in substance abusers is worth pursuing.

Several replication-extensions of the recent work might be considered with other antidepressant agents, other comorbid mood or anxiety disorders, and other substance use disorders. Several examples follow.

- Newer antidepressant agents: Most trials to date have involved tricyclic antidepressants. Trials with newer agents, such as specific serotonin uptake inhibitors, seem worthwhile because these may have fewer side effects and a greater margin for safety, or exert a stronger effect on depression or substance abuse or both.

- Depressed cocaine abusers: Given the inconsistent results of desipramine trials in unselected cocaine abusers, a trial of desipramine in selected depressed cocaine abusers would be useful. No such trial has been reported to date.

- Psychotherapy of depression: Recently developed short-term psychotherapy methods, cognitive therapy (Wright 1988; Elkin et al. 1989; Klein and Ross 1993), and interpersonal psychotherapy (Klerman et al. 1984; Elkin et al. 1989; Klein and Ross 1993) have demonstrated some efficacy in the treatment of depression. These warrant testing as alternatives to pharmacotherapy in depressed substance abusers because of concerns about the risks of medication interactions with illicit substances.

- Combined pharmacotherapy and psychotherapy: The literature suggests that effective antidepressant medication treatment in depressed substance abusers only partially reduces the drive to use drugs or alcohol. This suggests that antidepressants might best be applied as part of a multifaceted treatment strategy. For example, antidepressants could be studied in combination with promising techniques such as cognitive-behavioral therapy (Woody et al. 1983), relapse prevention (Carroll et al. 1991; Daley and Marlatt 1992; Marlatt and Gordon 1985; McAuliffe and Chi'en 1986; Rawson et al. 1991), cue extinction (Childress et al. 1992), or contingency management (Higgins et al. 1993; Iguchi et al. 1988; Stitzer et al. 1992). A two-way factorial design is possible, crossing two levels of medication (placebo, antidepressant) with two levels of therapy (standard versus enhanced intervention). An elegant example of such a study in cocaine abusers not selected for depression has recently been published (Carroll et al. 1994).

A second important line of research would focus on improving methods of identifying "true" depression in substance abusers, including those who may still be actively using. Certainly, the ideal method is to conduct a psychiatric diagnostic interview after at least 2 to 4 weeks of abstinence. However, the ideal is often difficult to achieve. Many patients will have difficulty abstaining as outpatients, and inpatient stays may not be available to uninsured patients, for example, or too short to be useful, even with insurance. In addition, some patients will decline hospitalization for legitimate reasons such as work or family responsibilities.

Hypothesizing that features of the clinical history can be used to identify treatable depression, the authors have developed a special version of the Structured Clinical Interview for DSM, the SCID-Substance Abuse Comorbidity (SCID-SAC) (Nunes et al., in press), which elicits these features. They include whether the depression antedated the onset of substance abuse, whether it persisted during historical periods of abstinence (such as during an episode of successful treatment or a stint in jail), and the extent to which the depression is chronic or longstanding. Rounsaville and colleagues (1991) suggest that depression emerging during a period of stable substance use may be a valid criterion for selecting "true" depression. Hasin and colleagues have developed a highly detailed structured interview, the PRISM (Hasin et al. 1994), which elicits a number of historical features connecting substance use to comorbid mental disorders. Further study of the reliability and predictive validity of such historical features and of instruments such as the SCID-SAC and PRISM are needed. Clearly, better tools for sample selection will improve the power and precision of clinical trials of antidepressant agents in substance abusers.

Research should also be considered on biological tests that might aid in diagnosis. Unfortunately, biological tests for depression, such as the dexamethasone suppression test (DST), are still of very limited use, and lack sensitivity and specificity. The extensive literature on the DST in substance abusers (Kroll et al. 1983; Willenbring et al. 1984; Ravi et al. 1984; Khan et al. 1984; Abou-Saleh et al. 1984; Newsom and Murray 1983; Johnson and Perry 1986; Burch et al. 1986; Dackis et al. 1984, 1986; Zern et al. 1986), for example, shows that the DST is influenced by recent substance use, and therefore it is not very useful in distinguishing depression. However, better tests may become available. In addition, a nascent literature suggests that physiologic challenge with sodium lactate infusion (Baron et al. 1990; Cowley et al. 1989; George et al. 1989) may have promise for identifying panic disorder in alcoholics.

Finally, a number of research questions exist in the realm of services. If the approach to diagnosing and treating depression and other comorbid mental disorders is applied in drug treatment clinics in the community, what are the risk-benefit and cost-effectiveness ratios? Do the benefits outweigh the risks? How can a diagnostic-therapeutic enhancement be delivered efficiently, at a low enough cost to justify what may be marginal improvements in outcome? For example, having an experienced psychiatric diagnostician interview all patients

admitted to a substance use clinic and follow those with suspected comorbidity requires a substantial amount of the time of an expensive staff member. Could regular counselors use screening instruments to do the case finding during their routine contacts with patients? Answering this question calls for a straightforward design comparing the sensitivity and specificity of counselors' screenings, of different screening instruments instead of gold standard psychiatric interview, and the time and cost of the approaches.

Designs addressing risk-benefit and cost-effectiveness of treatment interventions are more problematic and require further methodologic development. The crux of the problem is that long-term treatment and followup are needed, but it is ethically difficult to justify randomizing depressed patients, for example, to a placebo control condition for 6 to 12 weeks when acute efficacy studies suggest that the depression would respond to treatment. Quasi-experimental designs, with careful attention to identifying and minimizing potential biases in nonrandomized control conditions, may be needed.

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