Variability in Treatment-Seeking Cocaine Abusers: Implications for Clinical Pharmacotherapy Trials

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Variability in cocaine abusers seeking treatment in terms of potential prognostic dimensions such as severity of dependence, route of administration, concurrent use or dependence on other drugs and alcohol, psychiatric comorbidity, treatment history, and many others, has been a long-recognized feature of this population. Consideration of hetero-geneity among cocaine abusers is important as it may point to treatment strategies for some subpopulations. For example, identification of subgroups with distinct clinical characteristics or who have differential response to treatment is useful, as it may point to specialized treatment strategies that may be effective for these subgroups or for patient-treatment matching. At the same time, however, patient heterogeneity often confounds the interpretation of data from many pharmacology and psychotherapy treatment trials conducted thus far, by introducing noise and decreasing power to detect treatment effects.

In considering the implications of patient variability for cocaine pharma-cotherapy trials, it should first be noted that no pharmacotherapies are universally effective. For example, methadone maintenance, by far the most effective treatment for opioid dependence, is not universally successful in retaining patients or affecting complete cessation of illicit opioid use (Lowinson et al. 1992). Although program characteristics are associated with a great deal of variability in outcome (Ball and Ross 1991), patient characteristics such as psychiatric severity is another important predictor of response to methadone maintenance treatment (McLellan et al. 1993; Rounsaville et al. 1982). Similarly, although naltrexone has had limited impact on the drug abuse treatment system because of compliance and retention issues, it nevertheless retains a place in the treatment system because it is successful with some types of patients, typically middle-class patients and those with less severe or less chronic opioid dependence (Rounsaville 1995). Thus, success profiling, i.e., identifying patient characteristics associated with optimal outcome in well-defined treatments, is an important strategy for enhancing the effectiveness of treatment by providing treatment primarily to those most likely to benefit from it. Evaluation of

patient-treatment interactions has become a cornerstone of research on psychosocial treatments for substance dependence, where main effects of one form of treatment over another are rare, and response to even the most effective psychosocial approaches is incomplete. Evaluation of patient-treatment interactions may be an underutilized strategy in medications development.

To illustrate how evaluation of variability in treatment response as a function of patient characteristics may lead to a more complete understanding of a treatment's effects and help make sense of apparently contradictory findings across different studies, two examples from recent clinical trials evaluating pharmacotherapy for cocaine dependence will be presented. The first example illustrates variations associated with patient characteristics as moderators of treatment response (variables that affect the strength or direction of treatment response); the second illustrates implications of a patient characteristic as a mediator of treatment response (a mediator is a variable that produces a relationship between the independent and dependent variable). In other words, mediators determine the nature or mechanism of a matching effect, and moderators determine the strength of a match (see Baron and Kenny 1986, and DiClemente et al. 1994 for a fuller description).

Example 1: Desipramine Treatment of Cocaine Dependence

Enormous excitement was generated by the initial promising findings concerning the effectiveness of tricyclic antidepressant treatment of cocaine dependence, first in an open trial (Gawin and Kleber 1984) and later in a randomized, double-blind, controlled trial (Gawin et al. 1989), which indicated significant reductions in cocaine use for desipramine compared to lithium and placebo. However, later studies conducted in other settings with different patient populations generally failed to find main effects supporting the effectiveness of desipramine among the general population of cocaine abusers, including those on methadone maintenance (Arndt et al. 1992; Kosten et al. 1992; Weddington et al. 1991). What happened? While this set of studies underlines the importance of replicating a treatment's effects in multiple studies before it is widely adopted, it also highlights the point that variations in a medication's effectiveness may be explained by the changing nature of the patient population.

To illustrate this, findings from the Gawin study will be compared with outcomes from a later randomized controlled trial of desipramine and

cognitive-behavioral relapse prevention, in a 2X2 design, as treatment for 121 cocaine abusers (Carroll et al. 1994*a*). This study was conceived in part as a replication of the initial promising findings of desipramine, but more importantly to extend those findings by systematically evaluating the effectiveness of psychotherapy as well. Therefore, the authors strove for a high level of methodological rigor in specifying and implementing both pharmacologic and psychotherapeutic aspects of treatment. For example, design features of the study included:

- Random assignment to treatment condition (desipramine plus relapse prevention treatment, desipramine plus clinical management, placebo plus relapse prevention, or placebo plus clinical management.

- Careful selection of appropriate control conditions for both the desipramine treatment (placebo) and the cognitive-behavioral psychotherapy (clinical management, which provided nonspecific aspects of psychotherapy but not active ingredients of the coping skills treatment).

- Specification of all aspects of treatment delivery in manuals (Carroll et al. 1991*b*; Fawcett et al. 1987).

- Adequate duration of treatment (12 weeks) to allow emergence of specific effects of both pharmaco- and psychotherapy.

- Avoiding confounding of treatment through limiting subjects' exposure to nonstudy treatments.

- Delivery of treatments by experienced therapists committed to the type of treatment they conducted (doctoral-level psychologists conducted the cognitive-behavioral relapse prevention treatment, and postresidency psychiatrists conducted clinical management).

- Extensive therapist training, which included both a 2-day didactic seminar and successful completion of at least one closely supervised training case.

- Efforts to improve adherence to manual guidelines and prevent drift through the main phase of the study, which included regular meetings with therapists in each condition to discuss case material and review session videotapes.

•Close monitoring of both forms of treatment, which included regular assessment of medication plasma levels and process assessment of session videotapes by independent raters, which showed the relapse prevention and clinical management treatments were discriminable (Carroll et al., in press).

•Multidimensional assessment of outcome from multiple sources, including clinical evaluators blind to treatment condition (Carroll et al. 1994*a*).

•1-year followup, where 80 percent of all patients randomized to treatment were interviewed at least once (Carroll et al. 1994*b*).

Results: Main and Interaction Effects

After 12 weeks of treatment, subjects as a group showed significant improvement on most outcome measures, including cocaine use and psychosocial outcomes. However, significant main effects of desipramine, relapse prevention, or their interaction were not seen on primary outcomes, which included urine toxicology screens, frequency of cocaine use in the past 30 days, and Addiction Severity Index (ASI) cocaine composite scores (see Cacciola et al., this volume). Therefore, despite the authors' clinical sense of marked variations in outcome among patients in the sample, outcomes appeared similar across treatments when the sample was evaluated as a whole. However, there were data from two previous studies suggesting that severity may be an important moderator of treatment response in cocaine abusers. Therefore, by not evaluating outcome with respect to severity differential treatment effects may be masked. The first of these studies reported on a 1-year followup from a diagnostic study of 298 treatment-seeking cocaine abusers (Carroll et al. 1993*b*), which found that the most consistent and robust predictor of functioning was the subjects' severity of cocaine dependence at baseline (as assessed by total number of DSM-III-R cocaine dependence criteria endorsed). The second study, pointing to severity as a moderator of treatment response in cocaine abusers, was a pilot psychotherapy study that compared two forms of psychotherapeutic treatments: cognitive-behavioral relapse prevention (RP) or interpersonal psychotherapy (IPT) (Carroll et al. 1991*a*). In that study, while again there were no main effects of psychotherapy type on cocaine outcomes, marked differences in response to treatment were found after stratifying for baseline severity: At low levels of severity subjects both IPT and RP fared about equally in achieving at least 3 weeks abstinence during treatment. However, at high levels of severity, subjects in RP were significantly more likely to attain 3

weeks of abstinence than high-severity patients treated with IPT (54 percent versus 9 percent).

Thus, as previous research suggested that severity of cocaine use may be an important moderator of treatment response in cocaine abusers, data from the relapse prevention-desipramine study evaluating interactions of treatment type by severity were reanalyzed. However, severity was not defined a priori as a factor. The sample was stratified into three levels (to sharpen contrasts between high and low severity use): low (1 to 2.5 g of cocaine per week at baseline), moderate (2.6 to 4.4 g per week), and high severity (more than 4.5 g per week). Univariate ANOVAs indicated this classification of severity was associated with other indicators, including chronicity of use and route of administration.

Results of the exploratory 2X2X3 (medication by psychotherapy by severity) ANOVAs are illustrated in figure 1. There were consistent severity by psychotherapy (relapse prevention versus clinical management) interactions, with higher severity subjects who received relapse prevention reporting significantly longer consecutive periods of abstinence, better retention, and fewer cocaine-positive urine toxicology screens.

There were no significant pharmacotherapy (desipramine/placebo) by severity interactions for primary outcomes for the full sample. However, for the subsample that completed at least five sessions and therefore had greater opportunity for emergence of medication effects, there was a significant interaction between medication and baseline severity. Low-severity subjects treated with desipramine had significantly longer periods of consecutive abstinence than low-severity subjects taking placebo; for moderate and high-severity subjects desipramine and placebo were comparable in effectiveness.

Comparison With Other Desipramine Studies

Thus, in this study desipramine appeared most effective among the least severe cocaine abusers. These findings were thus inconsistent with the data reported by Gawin and colleagues (1989), which suggested a robust main effect for desipramine. As these two studies were conducted in the same clinic, by overlapping groups of investigators, using parallel sets of procedures and inclusion/exclusion criteria, the differences in desipramine effects is puzzling, until characteristics of the two samples are compared: Subjects in the Gawin and colleagues 1989 study were

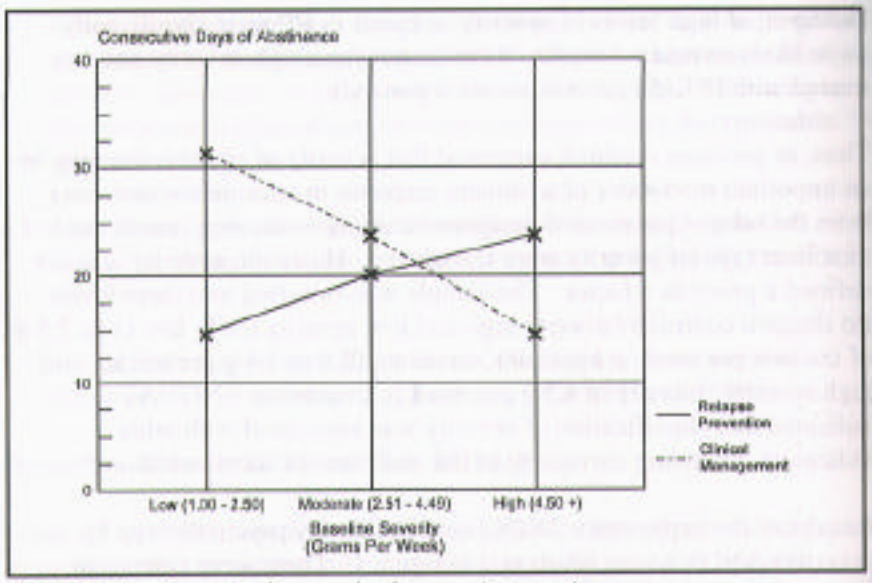

FIGURE 1. *Severity by psychotherapy interaction.*

KEY: Abstinence initiation in treatment N = 110.

recruited between 1984 and 1987 during the burgeoning of the cocaine epidemic, while the Carroll and colleagues 1994 study recruited patients between 1987 and 1991, a period characterized by rapid shifts in the treatment-seeking population and increasing predominance of freebase and crack use.

As indicated in table 1, the two subject samples differed on a number of dimensions. The Gawin sample included fewer blacks and Latinos, more patients who were employed, and more intranasal and fewer freebase users. Subjects in the Gawin sample also reported using fewer grams of cocaine per week on average, and had approximately half the rate of Axis I disorders with respect to the Carroll and colleagues 1994 study. Thus, it appears that subjects in the Gawin study, which suggested the general effectiveness of desipramine, were most similar to the less severe subsample of the authors' study (the only subgroup for which desipramine was found to have an effect on cocaine use). Similarly, Arndt and associates (1994) reported a desipramine effect among methadone-maintained cocaine abusers only when those with concurrent antisocial personality were excluded. Antisocial personality disorder has been associated with severity of cocaine abuse (Carroll et al. 1993*a*). Thus, exclusion of those with antisocial personality disorder in

TABLE 1. *Variations in sample characteristics, Gawin et al. (1989) compared to Carroll et al. (1994a*)

Characteristic	Gawin et al. (N = 72)	Carroll et al. (N = 121)
Percent female	24%	27%
Percent white	76%	46%
Percent employed	(mean 10 yr)	52%
Percent single/divorced	71%	71%
Mean age	29	29
Mean cocaine g/wk	3.6	4.4
Route of administration		
Percent intranasal	50.0	29.0
Percent freebase	32.0	62.0
Percent intravenous	18.0	9.0
Lifetime rates, DSM-III-R psychiatric disorders		
Any Axis I disorder	14%	26%
Any affective disorder	11%	20%
Any anxiety disorder	*	13%
Antisocial personality	*	49%
Alcohol dependence	*	33%

NOTE:* Indicates not reported.

the Arndt and colleagues 1994 sample may have left a less severe subsample that, like the less severe sample in the authors' study, was more responsive to desipramine treatment.

Example 2: Desipramine Treatment of Depressed Cocaine Abusers

The growing literature on desipramine treatment of cocaine dependence provides another example of how variations in sample characteristics across studies may influence conclusions about a medication's effectiveness. Recall that there are two principal rationales for anti-depressant treatment of cocaine dependence, each targeted to different groups. First, desipramine may reverse cocaine-induced disregulation in reward mechanisms, hence cocaine craving and use, in the general population of cocaine abusers (Gawin and Kleber 1984; Gawin et al. 1989). The example above suggests that severity may be a moderator of this effect. However, a second rationale for desipramine is that it may work through treating depression in the subgroup of cocaine abusers who may be attempting to self-medicate depressive symptoms (see Kosten

1989). Here, the presence of depression would serve as a mediating variable for desipramine effects (e.g., desipramine would work only for depressed subjects and reduction in depression would lead to reductions in cocaine use). This distinction is also important in relation to the inconsistent reports of the effectiveness of antidepressant treatment for cocaine abusers across studies, as variations in rates of depression across studies could affect conclusions about desipramine's effectiveness if it exerted effects primarily through an antidepressant mechanism or was differentially effective with depressed cocaine abusers (Carroll et al. 1995).

However, few studies have reported on the effectiveness of anti-depressants in reducing both cocaine use and depressive symptoms, or on differences in desipramine's effectiveness for general (nondepressed) versus depressed subpopulations. Giannini and colleagues (1986) reported a significant reduction in depression for cocaine addicts treated with desipramine in an open trial, but did not report on cocaine outcomes. As mentioned earlier, Gawin and colleagues (1989) reported that desipramine significantly reduced cocaine use regardless of whether patients were depressed. Weddington and colleagues (1991) found no effect of desipramine over placebo on either cocaine or depression outcomes; however, in that study, desipramine doses may have been subtherapeutic. Among methadone-maintained opioid addicts who also abused cocaine, Arndt and colleagues (1992) reported that desipramine improved psychological functioning but did not affect cocaine use. Ziedonis and Kosten (1991) found that depressed methadone-maintained opiate addicts showed significant reduction in cocaine use when treated with amantadine or desipramine compared with placebo, although these medications were not effective in reducing cocaine use for nondepressed subjects. They also reported that neither desipramine nor amantadine reduced depressive symptoms significantly, a small increase in depressive symptoms was seen for those treated with placebo.

In the 1994 study, the rationale for use of desipramine was as an anticraving agent, intended to facilitate abstinence initiation in a heterogeneous sample of cocaine users. Thus, the initial analyses did not evaluate either (a) the effectiveness of desipramine as an antidepressant agent for depressed cocaine abusers, or (b) whether desipramine might have greater efficacy in reducing cocaine use among depressed patients. The data were therefore reanalyzed to address these issues. For these analyses, treatment response was assessed based on level of current depressive symptoms (rather than presence of a DSM-III-R depressive disorder) for several reasons: First, diagnosing affective disorders in current substance users is complicated because it is difficult to distinguish

transient, substance-induced symptoms from more enduring syndromes (Meyer 1986). Second, stringent guidelines for diagnosing affective disorders in cocaine users, which require a period of stable abstinence before symptoms can be counted as meeting criteria for affective disorders, may underestimate rates of depressive disorders in current cocaine abusers (Rounsaville et al. 1991). For example, although subjects' mean pretreatment Beck Depression Inventory (BDI) and Hamilton Rating Scale for Depression (HRSD) scores were 9.03 (SD = 6.36) and 7.66 (SD = 5.64), respectively, only 1 subject met criteria for a current and 17 (20.7 percent) for a lifetime diagnosis of major depressive disorder. This was in large part due to these subjects' chronic substance use histories, which typically began in early adolescence, with few periods of stable abstinence that would allow definitive assessment of psychiatric symptomatology independent of drug effects.

Thirty-seven subjects (35 percent) were identified as having at least mildly elevated depressive symptoms at baseline, defined by BDI scores of 8 or above, and HRSD scores of 7 or above. Beck identified a score of 8 or above as consistent with moderate depression (Beck and Beck 1972). While the HRSD has no standard scales for interpretation, Frank has proposed a cutoff of seven to indicate presence of partial or full expression of depression (Frank et al. 1991). The combination of the two criteria was used to provide a more reliable indicator of level of depressive symptoms and to identify a sample where independent evaluators' clinical impressions were consistent with patient self-reports of depressive symptoms. Compared to the 72 subjects who did not meet these criteria for elevated depressive symptoms, the 37 depressed subjects were significantly more likely to be female and white, which is consistent with recent studies evaluating gender (Griffin et al. 1989) and race (Ziedonis et al. 1994) differences in clinical samples of cocaine abusers. As expected, depressed subjects were significantly more likely to have a lifetime history of a major depressive episode (36 percent versus 15 percent). There were no differences between the depressed and nondepressed groups in terms of marital status, education, socioeconomic status, or treatment group assignment. Regarding severity of cocaine use, there were no differences between the depressed and nondepressed groups on frequency or quantity of cocaine use nor principal route of administration. However, the ASI cocaine composite score (see Cacciola et al., this volume) suggested significantly higher severity for the depressed group. Because of the baseline differences between depressed and nondepressed subjects with respect to ASI cocaine composite scores and gender, the analyses described below were repeated controlling for these two variables. Neither gender nor baseline cocaine use had a significant main effect on cocaine or depression outcomes, nor did

controlling for these variables alter the patterns or significance of the findings presented below.

Treatment Response in Depressed Versus Nondepressed Cocaine Abusers

Depressive symptoms dropped significantly more for the depressive subgroup than the nondepressed subgroup as measured by both the BDI and the HRSD, regardless of treatment condition. As shown in table 2, although the depressed subjects were comparable to or more severe than the nondepressed users on baseline measures of cocaine use, regardless of treatment condition, the depressed subjects tended to accrue more days of consecutive abstinence than nondepressed subjects (25.1 versus 18.8 days, NS), and reported a higher percentage of abstinent days (0.86 versus 0.81, NS), although these differences were not statistically significant.

Table 2 also shows that depressed subjects treated with desipramine had a significantly greater reduction in depressive symptoms than placebo-treated depressed subjects, as measured by the BDI ($F = 3.80$, $p < 0.05$). Desipramine-treated subjects had a significant reduction in depressive symptoms, as measured by the HRSD, regardless of whether or not they were depressed ($F = 3.37$, $p < 0.01$). Relapse prevention treatment was not associated with greater reduction in depressive symptoms than clinical management for either the whole sample or the depressed subgroup.

For cocaine outcomes, desipramine was not associated with significant improvements over placebo for either the full sample or the depressed subgroup. However, there was a significant interaction for psychotherapy type and depression on some cocaine outcomes. Depressed subjects treated with relapse prevention reported significantly more days of consecutive abstinence than the depressed subgroup, which received clinical management (30.3 versus 20.2 days), while nondepressed

TABLE 2. *Cocaine and depression outcomes by treatment group (N = 109).*

	Treatment Group[1]					Significance	
	CM/DMI N = 25	RP/DMI N = 28	CM/PLA N = 27	RP/PLA N = 29	Overall mean	Main Effects	Interaction
Number of psychotherapy sessions[2], mean (sd)							
Euthymic	7.6 (3.3)	6.4 (3.9)	7.2 (3.7)	6.5 (3.5)	6.9 (3.6)		
Depressed	5.9 (3.2)	10.2 (2.8)	6.3 (2.9)	9.5 (4.0)	7.9 (3.6)		RP/DEP[3]
Cocaine Outcomes							
Consecutive days of abstinence, mean (sd)							
Euthymic	28.4 (27.6)	14.1 (11.9)	20.1 (15.5)	14.9 (11.9)	18.8 (11.9)		
Depressed	19.0 (18.7)	30.6 (19.1)	21.9 (26.2)	29.7 (24.7)	29.7 (24.7)		RP/DEP[3]
Percent days abstinent[4], mead (sd)							
Euthymic	0.84 (0.15)	0.82 (0.14)	0.79 (0.23)	0.81 (0.19)	0.81 (0.18)		
Depressed	0.85 (0.12)	0.91 (0.06)	0.83 (0.11)	0.86 (0.15)	0.86 (0.10)		

KEY: 1 = CM = clinical management, DMI = desipramine, RP = relapse prevention, PLA = placebo, DEP = depression; 2 = Range is 1 to 12; 3 = Indicates significant ($p < 0.01$) interaction of psychotherapy condition with depression; 4 = Indicates percent days abstinent as percentage of total days in treatment; 5 = Indicates significant ($p < 0.05$) interaction of desipramine and depression.

TABLE 2. *Cocaine and depression outcomes by treatment group (N = 109) (continued).*

	Treatment Group[1]					Significance	
	CM/DMI N = 25	RP/DMI N = 28	CM/PLA N = 27	RP/PLA N = 29	Overall mean	Main Effects	Interaction
Depression Outcomes							
Beck Depression Inventory							
Euthymic							
Pretreatment	5.6 (4.9)	7.8 (6.6)	6.4 (5.7)	5.9 (4.7)	6.4 (5.4)		
Posttreatment	1.7 (2.5)	50. (6.9)	2.7 (3.2)	4.2 (6.0)	3.7 (5.6)		
Depressed							
Pretreatment	13.7 (4.5)	11.8 (3.8)	17.1 (5.5)	15.8 (4.0)	14.2 (4.7)	Time	
DMI/DEP[5]							
Posttreatment	4.3 (4.2)	3.8 (3.8)	10.6 (10.6)	4.8 (8.7)	6.2 (7.0)	DEP	DEP/Time
Hamilton Rating Scale for Depression							
Euthymic							
Pretreatment	5.6 (3.0)	5.2 (5.2)	5.4 (5.4)	4.9 (3.4)	5.2 (4.2)		
Posttreatment	3.2 (3.0)	4.6 (5.6)	4.5 (3.3)	5.1 (4.0)	4.4 (4.1)		
Depressed							
Pretreatment	11.4 (3.8)	13.4 (7.0)	12.9 (5.1)	10.3 (3.0)	12.2 (5.2)	Time	DMI/Time
Posttreatment	5.4 (3.7)	3.1 (2.4)	9.8 (6.4)	6.0 (5.9)	5.7 (4.9)	DEP	Dep/Time

subjects accrued more abstinence in clinical management (23.7 versus 14.6 days, F = 6.95, $p < 0.01$). While this pattern was also seen for percent days abstinent during treatment, the interaction was not statistically significant.

Thus, analyses of desipramine effects on depressed cocaine users suggested that desipramine was an effective antidepressant in this sample, but appeared to have little effect on cocaine use. There were, however, moderate correlations between reductions in depressive symptoms and cocaine use (range 0.20 to 0.35). The direction of the moderate cocaine depression relationship could not be determined from the data; that is, whether reductions in cocaine use led to improvements in depression or reduction of depression made it easier for patients to reduce their cocaine use or both. That these correlations were higher for patients who received desipramine compared to placebo suggests that the early but transient desipramine-associated reductions in cocaine use may have been associated with an antidepressant effect. To evaluate these relationships further and to explore the role of depression as a potential mediator of desipramine effects, further research, particularly desipramine trials that specify depression as an a priori matching variable (such as those described by Nunes, this volume) are needed.

RECOMMENDATIONS

Currently there is no medication that has been shown to be broadly effective for retaining cocaine abusers in treatment, nor in reducing their cocaine use. However, as illustrated in these two examples, there is growing evidence that available treatments may be more effective in some subgroups of cocaine abusers. Thus, rather than abandon current approaches because of their apparent modest effects in treating the general population of cocaine abusers, a more fruitful strategy may be identification of characteristics associated with differential response to treatment (that is, it may be better to effectively treat some cocaine abusers some of the time than no cocaine abusers none of the time). A crucial advance in this process would be more careful assessment and description of study samples, as well as examination of outcome variability as a function of selected patient characteristics. Moreover, a thorough description of study samples in terms of clinically important and theoretically relevant features would also provide an important means of facilitating comparison of outcomes across different studies conducted by different investigators.

A small set of potential moderating variables is listed below. First, however, it is important to note that in evaluating identifying matching variables, investigators much be cautious about collinearity among matching variables. Many key prognostic variables may be moderately to highly correlated among clinical samples of cocaine abusers. For example, as noted earlier, the data suggested that depression was associated with differential response to psychotherapy and pharmacotherapy; however, several other variables, particularly gender and race, were significantly associated with depressive symptomatology. Although our findings held even when controlling for these variables, it was not completely clear whether it was the presence of depressive symptoms, or another related variable, that was responsible for the observed interactions. Thus, in many cases it will be unclear whether it is the identified matching variable, or another correlated variable, that was responsible for the "match." Therefore, it should be noted that in the following list some variables may be highly associated with others.

1. Gender. While few studies have found gender effects in treatment response (McLellan et al. 1994), in most studies conducted to date, samples of women have been too small to conduct analyses of gender effects with adequate power. Female cocaine patients may differ from males on a number of clinically relevant variables that may be associated to outcome and treatment response (Griffin et al. 1989), including severity and chronicity of cocaine use, psychopathology, and social and family support.

2. Race. Some studies have found race to be a prognostic variable (Grabowski and Higgins 1992) for medication response in cocaine abusers. However, it is not yet clear to what extent characteristics associated with race in specific samples (e.g., socioeconomic status, source of referral, social supports) may account for apparent race effects.

3. Education and employment status. Education and employment have been among the more consistent predictors of treatment retention and response in the drug abuse treatment literature. Again, it is not clear whether these variables have a direct effect on treatment response or a more indirect effect through relationships with other moderators such as motivation for treatment, compliance, and so on.

4. Severity of cocaine dependence. Emerging evidence points to severity as an important prognostic indicator in general (Carroll et al. 1993*b*; McLellan et al. 1994), as well as a treatment-

matching variable (Carroll et al. 1994*a*). As there is likely to be high correla- tions between severity and other prognostic variables such as socio-pathy, family history, severity of psychosocial problems, age of onset, and so on, a more parsimonious strategy for evaluating this set of variables may be through multidimensional subtyping, a promising strategy developed in the alcohol field (Babor et al. 1992), which has been recently shown to generalize to cocaine abusers (Ball et al. 1995).

5. Route of administration. Nunes (this volume) reports data linking route of administration to antidepressant response, with better outcome for intranasal users than freebase/crack users. Again, route of administration may function as a proxy for a number of indicators, such as severity and chronicity of drug use, SES, and polysubstance use.

6. Primary drug and treatment setting. Findings based on individuals whose principal drug dependence diagnosis is cocaine may not generalize to samples composed of methadone-maintained opiate addicts who have developed secondary cocaine dependence, and vice versa, because of large differences in patterns and levels of psychopathology between opioid and cocaine populations (Rounsaville et al. 1991), reinforcement contingencies in the two treatment settings, and so on.

7. Comorbid alcohol and other drug use. Alcohol dependence frequently co-occurs with cocaine dependence (Regier et al. 1990) and has been associated with poorer prognosis (Carroll et al. 1993*b*). Several distinctive features of this subpopulation suggest specialized treatment strategies may be needed (Carroll et al. 1993*c*; Higgins et al. 1991).

8. Comorbid psychopathology. As noted earlier, differences in rates of comorbid disorders across studies are likely to produce differences in medication effects, particularly for psychotropic agents where effects may be mediated by the presence of psychopathology. At a minimum, any study sample should be described in terms of rates of current and lifetime DSM-IV disorders, particularly affective, anxiety, and antisocial personality disorder. Global ratings of psychopathology, such as the psychological section of the Addiction Severity Index (ASI), should also be included, as should continuous ratings of specific psychological symptoms, including depression and anxiety. The recent reports regarding the significance of sociopathy as a moderating variable for medication

response (Arndt et al. 1994) also suggests that categorical (e.g., DSM-IV diagnosis) and continuous ratings of sociopathy, such as the California Psycho-logical Inventory-So (Cooney et al. 1990; Megargee 1972) should also be included.

9. Motivation and contingencies. An individual's motivation for treatment and level of readiness to change may be an important determinant of treatment compliance and response (Prochaska et al. 1992). For example, Hall and colleagues (1991) found cocaine abusers' commitment to abstinence significantly associated with the likelihood of relapse. This important dimension has been infrequently assessed in clinical trials evaluating pharmacologic treatments for substance use disorders and may be helpful in identifying those individuals who are not likely to benefit from treatment in a given trial (Moras 1993). Similarly, the source of the individuals' treatment referral and powerful contingencies associated with some referral sources (e.g., employee assistance program, court system, child welfare) may play a role in their motivation for treatment and should be assessed and described.

SUMMARY

The two examples provided in this chapter suggest that the inconsistent findings across studies evaluating identical pharmacologic agents may be associated with variations in sample characteristics, particularly those associated with (a) general treatment responsiveness (e.g., severity of cocaine use, sociopathy), or (b) responsiveness to specific treatment strategies (e.g., rates of depression where antidepressant agents are evaluated). Describing study samples and evaluating treatment response along multiple dimensions, using a common set of standardized assessments, would be an important advance in understanding variation in subjects' response to medication effects and comparison of findings across different studies. Moreover, consistent description of study samples across a number of dimensions would set the stage for meta-analyses of patient-treatment interactions. Similarly, as new medications are developed and evaluated, variables that have a theoretical basis as mediators of treatment response should be identified and evaluated. It should be noted, however, that success profiling and matching research is more complex than the search for simple main effects (Finney and Moos 1986; Project MATCH Research Group 1993). In particular, adequate power to detect patient-treatment interactions requires much larger sample sizes than those that have to date characterized pharmacotherapy research for cocaine dependence. This strategy, however, is likely to

enhance the development of effective pharmacological interventions for this very challenging patient population as researchers' understand the complex processes associated with treatment seeking, retention, and outcome among cocaine abusers.

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ACKNOWLEDGMENTS

Support was provided by National Institute on Drug Abuse grant nos. RO1-DA04299, R18-DA06963, and P50-DA09241.

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