Predictors of Outcome in LAAM, Buprenorphine, and Methadone Treatment for Opioid Dependence

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This study examined (1) predictors of treatment outcome for opioid-dependent participants in a single-site controlled trial comparing methadone, buprenorphine, and LAAM treatments and (2) the extent to which various subpopulations of patients may have more successful outcomes with each medication. The relationships between patient demographics, drug use history, and psychological status and outcome measures of treatment retention, opiate use, and cocaine use were assessed. We believe this study to be the first to demonstrate that predictors of treatment success appear to be largely similar in LAAM, buprenorphine, and methadone treatment for opioid dependence. We did not find any factors that would strongly guide selection of one medication over others.

Keywords: opioid, treatment, buprenorphine, methadone, LAAM

Three opioid agonist medications are available in the United States as pharmacotherapeutic agents for the treatment of opioid dependence. Methadone, a full mu-opioid agonist, has been used in the treatment of opioid dependence since the 1960s and is the most widely used pharmacotherapy for opioid dependence in the United States (Dole & Nyswander, 1965). Levomethadyl acetate, or LAAM, also a full mu-opioid agonist, was approved by the U.S. Food and Drug Administration (FDA) for opioid substitution therapy in 1993 but has recently been withdrawn from the U.S. market by its manufacturer. Finally, buprenorphine, a partial mu-opioid agonist, was FDA-approved as a treatment for opioid dependence in 2002. These medications stabilize the neurobiological dysregulation of opioid-dependent patients and prevent them from experiencing opiate withdrawal symptoms (Leshner, 1998). Moreover, because of their affinity and cross-tolerance for the mu-opioid receptor, these medications can block the effects of exogenously self-administered opioids (e.g., heroin; Dole, 1988; Dole, Nyswander, & Kreek, 1966; Jasinski, Pevnick, & Griffith, 1978; Ling, Charuvastra, Kaim, & Klett, 1976).

The efficacy of these three medications in the treatment of opioid dependence has been repeatedly demonstrated in numerous controlled clinical trials. These studies have generally shown that when equieffective doses of these medications are provided, their efficacy in the treatment of opioid-dependence is comparable (Johnson et al., 2000). Indeed, these medications, especially when provided with ancillary behavioral therapy, have repeatedly been shown to produce marked reductions in illicit opioid use, criminal activity, and behavior that may place one at risk for infection with HIV, hepatitis, or other infectious diseases (Ball & Ross, 1991; Eissenberg et al., 1997; Johnson, Jaffe, & Fudala, 1992; Ling et al., 1998; Marsch, 1998; Schottenfeld, Pakes, Olveto, Zeidonis, & Kosten, 1997; Strain, Stitzer, Liebson, & Bigelow, 1993).

Although all three medications have opioid agonist properties, each of these three medications has been shown to have distinct differences relative to its use in the treatment of opioid dependence. Methadone has been the most extensively researched and most widely used medication in clinical settings (Ball & Ross, 1991). LAAM is a longer acting medication relative to methadone and, unlike methadone which must be administered daily, LAAM can be effectively administered thrice weekly (Ling et al., 1976). Buprenorphine, due to its partial mu-opioid agonist properties, has lower abuse potential and carries a lower risk for overdose relative to methadone and LAAM. Additionally, like LAAM, buprenorphine can be administered effectively on a less-than-daily basis (Bickel & Amass, 1995). Finally, unlike methadone and LAAM which in the United States must be provided to patients in a designated opiate treatment program, buprenorphine may be provided to opioid-dependent patients by qualified physicians in an office-based setting (although methadone is also offered in office-based settings in some other countries, Fiellin & O’Connor, 2002).
Given that each of these three medications has been shown to be efficacious and clinically useful in the treatment of opioid dependence, understanding whether various subpopulations of opioid-dependent patients have differential treatment outcomes with each of these medications is an important research endeavor. Indeed, clinical decision making regarding which medication to provide to an opioid-dependent individual presenting for treatment could be enhanced if significant predictors of treatment outcome with each of these three medications were identified.

A fairly extensive literature has reported on a number of significant predictors of treatment outcome for patients in methadone maintenance treatment. Although some mixed evidence exists, these studies have generally shown that longer retention in methadone treatment has been associated with being older, being married, and having a shorter history of opioid use, whereas poorer retention has been associated with a history of criminality and psychological and employment problems (Alterman, Rutherford, Cacciola, McKayam, & Boardman, 1998; Hser, Anglin, & Liu, 1990–1991; McLellan, 1983; McLellan, Luborsky, Woody, O’Bien, & Drul, 1983; Saxon, Wells, Fleming, Jackson, & Calsyn, 1996; Strain, Stitzer, Liebson, & Bigelow, 1998). Continued opiate use during methadone treatment has been associated with a longer history of opioid use and a longer history of cocaine use (Strain et al., 1998). Greater cocaine use during methadone treatment has been associated with a longer history of cocaine use and a greater number of psychological problems (Strain et al., 1998; Magura, Nwakese, & Demskey, 1998).

In contrast to the substantive literature reporting on predictors of treatment outcome in methadone treatment, only a few studies have examined predictors of treatment outcome in LAAM and buprenorphine treatment. These few studies have shown that fewer psychological problems are associated with longer retention in buprenorphine treatment, whereas fewer legal problems, greater employment problems, higher levels of novelty seeking, and higher levels of hostility (among women only) are associated with shorter retention in buprenorphine treatment (Helmus, Downey, Arfken, Henderson, & Schuster, 2001; Petry & Bickel, 1999, 2000). Additionally, having fewer drug users in one’s social network has been associated with greater cocaine abstinence during LAAM treatment (Wasserman, Stewart, & Deluuci, 2001).

The goals of the present study were twofold. First, we examined significant predictors of treatment outcome for opioid-dependent patients in each of methadone, buprenorphine, and LAAM treatments. In so doing, we believe that the study provides a novel and important contribution to the scientific literature because little information about significant predictors of treatment outcome is available for buprenorphine and LAAM treatments. Second, we examined differential predictors of treatment outcome in each of these three treatments. In so doing, we sought to learn whether various subpopulations of opioid-dependent patients may have more successful treatment outcomes with each of these medications. Such information may inform matching of opioid-dependent patients to treatments in which they may have the greatest likelihood of a successful treatment outcome. For the present study, we used data from the first and only study conducted to date to compare the relative efficacy of LAAM, buprenorphine, and methadone for opioid dependence in the context of a single controlled clinical trial. The present study was prospectively planned in that the analyses of predictors of treatment outcome were planned in advance of conducting the study. The primary outcome data from this trial have been reported elsewhere (Johnson et al., 2000).

Method

Participants

Participants were 165 opioid-dependent patients who participated in a single-site randomized controlled trial (Johnson et al., 2000). Eligibility criteria for participants included being between 21 and 55 years of age, having a Diagnostic and Statistical Manual of Mental Disorders (4th ed.; DSM–IV; American Psychiatric Association, 1994) diagnosis of opioid dependence, and having recently used opioids as evidenced by urine toxicology. Pregnancy or evidence of a serious psychiatric or medical condition requiring long-term medication, as assessed at the time of treatment intake, was exclusionary. Baseline characteristics of study participants are summarized in Table 1. This study was approved by the local institutional review board. After providing a complete description of the study to participants, we obtained written informed consent.

Study Design

Participants were stratified according to their age (<35 years or ≥35 years), race (White or other), sex (male or female), current cocaine use (yes or no), current marital status (married or not), and DSM–IV diagnosis of antisocial personality disorder (yes or no). They were randomly assigned on their day of enrollment to receive either methadone, LAAM, or buprenorphine (n = 55 per group).

Participants in the methadone condition received a maintenance dose of between 60 and 100 mg of methadone daily. (Note that a fourth group of participants received a low dose of methadone daily, 20 mg/day; however, this dosing condition was found to be less efficacious in the clinical trial and thus was not included in the present analysis). Participants in the LAAM condition received maintenance doses of between 75 and 115 mg on Mondays and Wednesdays and a 40% higher dose on Fridays to compensate for the longer time interval before the next dose. Participants in the buprenorphine condition received maintenance doses of between 16 and 32 mg on Mondays and Wednesdays and a 50% higher dose on Fridays. Note that a flexible dosing schedule for LAAM, buprenorphine, and methadone was used to achieve comparably effective doses across the three medication groups.

All dosing was double-blind and triple-dummy, such that participants received two oral and one sublingual solution on days of clinic attendance but only one solution contained active medication. All participants initially attended the research clinic daily for 2 weeks and received gradually increasing doses of medication. Participants who received active methadone and buprenorphine received daily doses of active medication during the first 2 weeks of the study, whereas participants randomized to LAAM received active doses every other day with alternating placebo doses during this time period. Subjects then participated in a maintenance phase for an additional 15 weeks during which they attended the clinic.
three times weekly and received take-home bottles of methadone (methadone group) or placebo methadone (buprenorphine and LAAM groups) on days they were not required to attend the clinic. On each of the three occasions they attended the clinic each week, participants also provided urine samples that were screened for the presence of opiates and cocaine metabolites (Enzyme Multiplied Immunoassay Technique; Dade Behring Diagnostics, San Jose, CA). Participants were provided with a double-blind rescue treatment if they showed a poor response to treatment. Participants receiving rescue treatment were switched to an equivalent dose of methadone and followed clinically. After the maintenance phase, all participants were then provided with an 11-week disposition period in which they were assisted in arranging longer term treatment in a nonresearch setting or could elect to have their medication dose gradually reduced to 0 mg. Details of the induction, dose increase, rescue treatment, and take-home recall procedures are reported in Johnson et al. (2000).

### Predictor Variables

At the time participants were enrolled in the study, trained research staff members used standardized clinical assessments to collect a variety of data from participants regarding their demographics, drug use history, and psychological status. Specifically, information about participants’ gender, education, race, marital status, and age was obtained. The Addiction Severity Index (ASI; McLellan, Luborsky, Woody, & O’Brien, 1980) was used to assess the number of days paid, and the number of days that legal income was received in the past 30 days. The Structured Clinical Interview for Personality Disorders (SCID; First, Spitzer, Gibbon, & Williams, 1996) was used to assess current dependence on various classes of drugs, including opiates, cocaine, alcohol, and sedatives, and the presence or absence of antisocial personality disorder. The Beck Depression Inventory (BDI; Beck, Ward, Mendelson, Mock, & Erbaugh, 1961) was used to assess depression levels, and the Symptom Checklist-90 (SCL-90; Derogatis, 1983) was used to assess hostility levels. These baseline characteristics of participants were used as predictor variables in the present analyses.

### Outcome Measures

Three outcome measures were selected in the present analyses: (a) mean length of retention in treatment, defined as the time of a participant’s admission to the study until the day of discharge from the study; (b) percentage of urine samples that were positive for opiates during the maintenance phase of the study; and (c) percentage of urine samples that were positive for cocaine during the maintenance phase of the study.

### Statistical Analyses

Pearson product–moment (r) correlational analyses between each predictor and outcome measure were initially conducted to determine which predictors and outcome measures were significantly correlated with one another and the magnitude of the correlation. Additionally, predictor variables were correlated with one another, and those predictors that were significantly correlated with one another were omitted. Specifically, past-30-day drug use measures from the ASI were significantly correlated with SCID drug dependence diagnoses and thus were omitted from subsequent analyses (Pedhazer, 1982). This process reduced the number of predictor variables from an initial 21 to a final total of 17 variables.

Univariate multiple regression analyses were then conducted to examine the unique contributions of the predictors to each outcome measure within each medication group. Cox regression analysis was used to determine the relationship between the predictors and the outcome measure of treatment retention. Cox regression was selected because it is a semiparametric survival method that readily assesses the ability of both continuous and dichotomous predictor variables to increase or decrease the likelihood of some
hazard (in this case, treatment dropout). The other outcome mea-
sures were assessed via least-squares regression models.

Finally, interaction tests were conducted to examine differential
effects of covariates (predictors) across each medication group for
each outcome measure. SAS version 6.12 was used for all analyses
(PROC CORR, PROC REG, and PROC PHREG procedures; SAS
Institute, Cary, NC). Results were considered to be statistically
significant at \( p \) values of .05 or less. Because of the exploratory
nature of this study, trends that did not reach statistical significance
(\( p \) values of between .05 and .10) are also reported (Bendel &
Afifi, 1977).

Results

Correlational Analyses of Predictors and Outcome
Measures

Table 2 presents the results of correlational analyses
between each predictor variable and each outcome measure
for each of the three medication groups. Pearson product–
moment correlation coefficients (\( r \)) values are presented to
 denote the magnitude of the relationships between predictor and outcome variables for each condition.

Predictors of Outcome Within Each Medication
Group

Table 3 presents results from univariate regression anal-
yses that examined the unique contributions of the predic-
tors to each outcome measure within each medication
group. Risk ratio values (reflecting change in risk for the
treatment dropout outcome measure given a predictor vari-
able) are presented in the first three columns of Table 3. Risk ratio values are dependent on the unit of the predictor variable and are interpreted as the change in risk for treatment dropout with a one unit change of the predictor variable; larger changes in the predictor variable predict larger
changes in risk for treatment dropout. Beta estimates are
also presented in this table for the opiate- and cocaine-
positive outcome measures to denote the degree to which a
given variable predicted outcomes after accounting for the
impact of other predictor variables (i.e., the degree to which a predictor variable increased or decreased the likelihood of opiate- or cocaine-positive results). The percentage of variance accounted for by each predictor variable on the percentage opiate-and cocaine-positive outcome measures is also presented in Table 3.

LAAM treatment. Four variables accounted for a signif-
ificant proportion of variance in the percentage of opiate-
positive results in the LAAM condition. Being cocaine-
dependent was a predictor of a higher percentage of opiate-
positive results. Being married was a predictor of a lower percentage of opiate-positive results. Higher levels of de-
pression were also predictive of a lower percentage of opiate-positive results. Being employed was predictive of a lower percentage of opiate-positive results, accounting for the largest percentage of variance (12.88%) on this outcome measure. Two nonsignificant trends were also observed: A greater number of months of alcohol use was a predictor of

<table>
<thead>
<tr>
<th>Predictor variable</th>
<th>LAAM</th>
<th>Methadone</th>
<th>Buprenorphine</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. years of education</td>
<td>0.23</td>
<td>-0.14</td>
<td>-0.33</td>
</tr>
<tr>
<td>Race (White)</td>
<td>0.04</td>
<td>-0.10</td>
<td>0.03</td>
</tr>
<tr>
<td>Marital status (married)</td>
<td>-0.25</td>
<td>-0.24</td>
<td>0.01</td>
</tr>
<tr>
<td>Current barbiturate use in life</td>
<td>-0.19</td>
<td>-0.20</td>
<td>-0.09</td>
</tr>
<tr>
<td>No. months cocaine used in life</td>
<td>-0.11</td>
<td>-0.11</td>
<td>-0.04</td>
</tr>
<tr>
<td>No. months other drug use in life</td>
<td>-0.14</td>
<td>-0.14</td>
<td>-0.07</td>
</tr>
<tr>
<td>No. months alcohol use in life</td>
<td>-0.13</td>
<td>-0.16</td>
<td>0.03</td>
</tr>
<tr>
<td>Age (mean yrs)</td>
<td>-0.15</td>
<td>-0.16</td>
<td>-0.06</td>
</tr>
<tr>
<td>Employment status (employed)</td>
<td>-0.31</td>
<td>-0.32</td>
<td>-0.13</td>
</tr>
<tr>
<td>Current sedative dependence (yes)</td>
<td>0.00</td>
<td>0.00</td>
<td>0.01</td>
</tr>
<tr>
<td>Current alcohol dependence (yes)</td>
<td>0.09</td>
<td>0.09</td>
<td>0.04</td>
</tr>
<tr>
<td>Symptoms checklist (SCL-90-R)</td>
<td>0.14</td>
<td>0.15</td>
<td>0.06</td>
</tr>
<tr>
<td>Antisocial personality disorder (yes)</td>
<td>0.24</td>
<td>0.25</td>
<td>0.12</td>
</tr>
</tbody>
</table>

*Values in bold indicate \( p \) \leq .05, \( \beta \) = levomethadyl acetate; SCL-90-R = Symptoms Checklist (Derogatis, 1983).
Table 3
Results of Within-Group Regression Analyses and Interaction Tests*

<table>
<thead>
<tr>
<th>Predictor variable</th>
<th>Treatment Dropout</th>
<th>Percentage Opiate-Positive Results</th>
<th>Percentage Cocaine-Positive Results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LAAM RR</td>
<td>Methadone RR</td>
<td>Buprenorphine RR</td>
</tr>
<tr>
<td>No. years of</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>education</td>
<td>0.789</td>
<td>1.055</td>
<td>0.850</td>
</tr>
<tr>
<td>Race (White)</td>
<td>0.938</td>
<td>0.572</td>
<td>1.026</td>
</tr>
<tr>
<td>**Marital status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(married)</td>
<td>0.477</td>
<td>0.673</td>
<td>0.682</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>1.302</td>
<td>1.212</td>
<td>1.414</td>
</tr>
<tr>
<td>**Beck Depression</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inventory score</td>
<td>0.987</td>
<td>1.013</td>
<td>0.982</td>
</tr>
<tr>
<td>No. months cocaine</td>
<td>1.001</td>
<td>1.008</td>
<td>1.005</td>
</tr>
<tr>
<td>use in life</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. months heroin</td>
<td>1.001</td>
<td>1.003</td>
<td>0.998</td>
</tr>
<tr>
<td>use in life</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>**No. months</td>
<td>1.009</td>
<td>1.000</td>
<td>1.001</td>
</tr>
<tr>
<td>alcohol use in</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>life</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. months</td>
<td>0.001</td>
<td>1.014</td>
<td>1.045</td>
</tr>
<tr>
<td>sedative use in</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>life</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (mean yrs)</td>
<td>0.948</td>
<td>1.013</td>
<td>0.915</td>
</tr>
<tr>
<td>**Employment status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(employed)</td>
<td>0.789</td>
<td>1.211</td>
<td>0.596</td>
</tr>
<tr>
<td>No. days paid</td>
<td>1.006</td>
<td>1.030</td>
<td>0.986</td>
</tr>
<tr>
<td>employment in</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>past 30</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current alcohol</td>
<td>0.535</td>
<td>0.908</td>
<td>1.981</td>
</tr>
<tr>
<td>dependence (yes)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current sedative</td>
<td>1.031</td>
<td>0.900</td>
<td>1.286</td>
</tr>
<tr>
<td>dependence (yes)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current cocaine</td>
<td>2.029</td>
<td>5.758</td>
<td>2.032</td>
</tr>
<tr>
<td>dependence (yes)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antisocial</td>
<td>1.545</td>
<td>1.700</td>
<td>0.786</td>
</tr>
<tr>
<td>personality disorder (yes)</td>
<td>1.002</td>
<td>1.050</td>
<td>1.023</td>
</tr>
</tbody>
</table>

Note. Treatment retention was reported in Table 2, while treatment dropout is reported in this table, because the reported survival analysis reversed the direction of the relationships. LAAM = levomethadyl acetate, RR = risk ratio value; SCL-90 = Symptoms Checklist-90 (Derogatis, 1983).
*Values in bold indicate $p \leq .10$, and values in bold and underlined indicate $p \leq .05$ from within-group univariate regression analyses.
**Predictor variable names preceded by a double asterisk denote trends for interactions ($p \leq .10$) between predictors and the outcome measure of percentage of opiate-positive results during test of interactions. In all four such cases, the LAAM and buprenorphine conditions showed different trends.
a higher percentage of opiate-positive results and being White was a predictor of a lower percentage of opiate-positive results.

Three variables accounted for a significant proportion of variance in the percentage of cocaine-positive results. Having a higher level of depression predicted a lower percentage of cocaine-positive results. Having a greater number of months of cocaine use in one’s lifetime and meeting criteria for cocaine dependence predicted a greater percentage of cocaine-positive results, with this latter variable accounting for the largest percentage of variance (32.04%) on this outcome measure. Also, one nonsignificant trend emerged, such that a higher level of hostility predicted a lower percentage of cocaine-positive results.

No predictor variables were shown to significantly alter the chance of treatment dropout in the LAAM condition; however, four nonsignificant trends emerged. Specifically, a trend was observed such that both having a greater number of years of education and being an older age predicted better treatment retention. Also, a trend was observed such that having a greater number of months of alcohol use in one’s lifetime predicted poorer treatment retention, as did cocaine dependence, which had the highest risk ratio for treatment dropout (RR = 2.029).

Methadone treatment. No predictor variables accounted for a significant proportion of variance in the percentage of opiate-positive results in the methadone condition; however, two nonsignificant trends were observed. The first trend was that being dependent on alcohol predicted a higher percentage of opiate-positive results. The second trend was that being White predicted a lower percentage of opiate-positive results and accounted for the largest percentage of variance (6.55%) on this measure.

Four predictors accounted for a significant proportion of variance in the percentage of cocaine-positive results. Both the presence of antisocial personality disorder and high levels of hostility predicted a greater percentage of cocaine-positive results. Having a greater number of months of cocaine use and being cocaine-dependent both predicted a higher percentage of cocaine-positive results, with the latter variable accounting for the largest percentage of variance (38.42%) on this outcome measure. Also, one nonsignificant trend emerged such that being married predicted a lower percentage of cocaine-positive results.

No predictor variables were shown to alter the chance of treatment dropout in the methadone condition; however, two nonsignificant trends emerged. Specifically, these trends showed that older age predicted better treatment retention, whereas a greater number of months of cocaine use and cocaine dependence predicted poorer treatment retention, with the latter variable having the highest risk ratio for treatment dropout (RR = 2.032).

Buprenorphine treatment. Three predictor variables accounted for a significant proportion of variance in the percentage of opiate-positive results in the buprenorphine condition. Both being male and having a higher number of paid days in the last 30 days predicted a greater percentage of opiate-positive results. Having higher levels of depression predicted a lower percentage of opiate-positive results and accounted for the largest percentage of variance (13.05%) on this outcome measure.

Three predictors accounted for a significant proportion of variance on the outcome measure of percentage of cocaine-positive results. Being married predicted a lower percentage of cocaine-positive results. Having a greater number of months of cocaine use in one’s lifetime predicted a higher percentage of cocaine-positive results, as did being cocaine-dependent, which accounted for the largest percentage of variance (34.57%) on this outcome measure.

No predictor variables were shown to alter the chance of treatment dropout in the buprenorphine condition; however, three nonsignificant trends were evident. These trends showed that older age predicted better treatment retention, whereas a greater number of months of cocaine use and cocaine dependence predicted poorer treatment retention, with the latter variable having the highest risk ratio for treatment dropout (RR = 2.032).

Differential Predictors of Outcome Across Medication Groups

Table 3 also presents results from analyses examining interactions between predictors and each medication group for each outcome measure. No statistically significant interactions were observed between predictor variables and medication conditions on any of the three outcome measures.

Four nonsignificant trends for interactions were observed between predictors and the LAAM and buprenorphine conditions in percentage of opiate positive results. Specifically, a trend was observed such that being married was a predictor of having a lower percentage of opiate-positive results in LAAM condition but not in the buprenorphine condition. Additionally, although higher levels of depression were significant predictors of a lower percentage of opiate-positive results in both the LAAM and buprenorphine conditions, a trend was observed such that the predictive ability of this variable was greater in the buprenorphine condition. Another trend showed that having a greater number of months of alcohol use in one’s lifetime was a predictor of having a higher percentage of opiate-positive results in the LAAM condition but not in the buprenorphine condition. The final trend showed that being employed was a predictor of a lower percentage of opiate-positive results in the LAAM condition but not in the buprenorphine condition. No trends were observed between predictors and the LAAM and methadone medication conditions or the methadone and buprenorphine medication conditions.

Discussion

In the present study, we had two primary goals: (a) to examine predictors of multiple measures of outcome within each of the methadone, buprenorphine, and LAAM treatments for opioid dependence because a paucity of research is available in the scientific literature addressing this clinically important issue and (b) to examine whether different variables predicted treatment outcome across these three
pharmacotherapeutic interventions. The data from the present study were obtained from the first study to compare the relative efficacy of these three medications in a single-site controlled clinical trial in which participants were randomly assigned to treatment conditions and stratified on key variables that have been previously shown to influence treatment outcome.

Correlational analyses revealed that numerous characteristics of patients at the time of their treatment intake were significantly associated with treatment outcome. Correlational analyses were primarily important for identification of the strength of the relationship between patient characteristics and treatment outcome. Results of regression analyses, however, are more clinically useful, because they reveal the unique contribution of each patient characteristic in predicting treatment outcome, and, indeed, not all of the significant predictor-outcome relationships observed in correlational analyses remained significant in regression analyses.

A total of 14 predictors either significantly predicted treatment outcome or showed nonsignificant trends with treatment outcome. An interesting and clinically important finding from these analyses was the tendency for predictor generally overlapped across medication groups, and no significant difference was noted in its predictive ability across groups. Although we expected that predictors of treatment outcome could differ for buprenorphine treatment, because of its partial agonist activity compared with treatment with full agonists, results suggest that buprenorphine largely functions like or is influenced by patient variables in a similar manner as pure agonist treatments. We will first focus our discussion on the relationships observed between predictors and outcome variables. We will then comment on the 4 predictors that showed a trend to differentially predict treatment outcome across the three pharmacotherapeutic interventions but that did not reach statistical significance.

**Significant and Nonsignificant Trends for Predictors of Treatment Outcome From Univariate Tests**

Being married and employed significantly predicted better treatment outcomes on several measures. This finding is consistent with previous reports showing that these variables significantly predict outcomes in methadone treatment (McLellan, 1983; Petry & Bickel, 2000; Saxon et al., 1996). Both being employed and being married may function as protective factors in that both provide alternative, nondrug-related sources of reinforcement for a patient.

A greater number of months of cocaine use and cocaine dependence both emerged as strong predictors of poorer treatment outcomes. These findings may underscore the importance of providing enhanced interventions targeting cocaine use among patients in treatment for opioid dependence. Consistent with this suggestion are the findings of prior research that provision of voucher-based reinforcement contingent on cocaine abstinence to opioid-dependent patients with comorbid cocaine dependence (Silverman et al., 1996; Silverman et al., 1998; Silverman, Chutuape, Bigelow, & Stitzer, 1999) can markedly improve outcomes during treatment for opioid dependence.

Higher levels of depression predicted better treatment outcomes on measures of both cocaine and opiate use. This result may appear somewhat surprising in light of prior results showing that patients with comorbid psychiatric problems generally have poorer treatment outcomes (McLellan et al., 1983, 1986). However, the relationship between psychiatric comorbidity and drug treatment outcomes is complex. That is, although psychiatric problems often predict poorer treatment outcomes, this has not been the case when enhanced therapeutic interventions focused on mental health have been provided to patients as part of their substance abuse treatment. Interestingly, patients with comorbid psychiatric problems (in particular, depressive symptoms) stay longer and become more invested in treatment when ancillary services addressing their mental health status are part of their substance abuse treatment; however, this same group of patients has been shown to have poorer treatment outcomes when only standard substance abuse treatment, without mental health treatment, is provided (Agost, Nunes, Stewart, & Quitkin, 1999; Broome, Flynn, & Simpson, 1999; Friedman & Glickman, 1987; Joe, Brown, & Simpson, 1995). If a patient in the present study showed any evidence of psychiatric concerns, they were evaluated by a counselor who then arranged for further evaluation and treatment with an onsite psychiatrist or other mental health professional. Ongoing psychiatric treatment continued to be provided as needed to such patients. This interesting finding has important clinical implications and may underscore the benefit of concurrently providing both drug abuse and mental health treatment services to patients with cooccurring disorders.

Both antisocial personality and hostility predicted greater cocaine-positive results. Personality disorders in general, and antisocial personality disorder in particular, have previously been associated with poorer retention in treatment for opioid dependence (Rounsaville, Kosten, Weissman, & Kleber, 1986; Woody, McLellan, Luborsky, & O’Brien, 1995). Additionally, antisocial personality has been shown to be correlated with hostility (Han, Weed, Calhoun, & Butcher, 1995), and hostile personality traits have also been associated with poorer treatment retention in a variety of substance abuse treatment settings (Petry & Bickel, 2000). The present study extends this finding by demonstrating that antisocial and hostile personality traits may also predict cocaine use. Patients with antisocial and hostile personality disorders may have poorer coping styles (Petry & Bickel, 2000; McCormick & Smith, 1995), which may affect their treatment outcome.

Male patients had better outcomes in opiate use than female patients. Although gender has previously been shown to be a weak predictor of outcome in methadone treatment, little research has explored this issue in buprenorphine or LAAM treatment. Further studies are needed to identify the conditions under which this effect may be replicated. Additionally, patients with a greater number of paid days in the past 30 days at the time of treatment intake...
had poorer outcomes on measures of opiate use, suggesting that their greater availability of income may have led to a greater consumption of opiates. This may appear contradictory to the finding that being employed was associated with better treatment outcomes. This finding may, in part, be due to patients reporting paid days that included payment for work from both legal and nonlegal activities. Future research could seek to discern this and to also explore whether financial management training and developing alternative strategies for managing and using money as part of counseling interventions could positively impact abstinence during treatment.

In addition to the significant predictors of treatment outcome described above, a number of nonsignificant trends for predictors of treatment outcome were evident. Specifically, a trend emerged such that being older was predictive of better treatment outcome. Older patients likely have a longer history of substance abuse and a greater number of problems as a result of such drug abuse and may accordingly have a greater motivation for treatment for their substance abuse problems. Another trend that emerged was that a greater number of years of education also predicted greater retention. The relationship between years of education and treatment outcome has largely been unexplored in the published literature on methadone treatment and, to our knowledge, has never been explored in LAAM or buprenorphine treatment. It is plausible that patients who have spent more time receiving an education may have more sources of non-drug-related reinforcement. Moreover, White patients showed a trend for lower percentage of opiate-positive results than other racial groups. Prior findings regarding the relationship between race and treatment outcome in the methadone treatment literature have been equivocal, with some studies showing slightly improved treatment outcomes for White patients and some studies showing slightly improved treatment outcomes for African American patients (Saxon et al., 1996). Further research is needed to explicate the relationship between race and treatment outcomes and the extent to which race may be a surrogate marker for other variables. However, at this time, race does not appear to be a strong and consistent predictor of treatment outcome, and this finding should be interpreted with caution. Finally, trends emerged showing that both a greater number of months of alcohol use and alcohol dependence were both predictive of poorer treatment outcomes. As with comorbid cocaine use, addressing comorbid alcohol use as part of treatment for opioid dependence may enhance treatment outcomes. Indeed, prior research has shown that providing disulfiram (Antabuse) medication to opioid-dependent persons with comorbid alcohol and cocaine abuse (Petrikis et al., 2000) can improve outcomes during treatment for opioid-dependence.

**Differential Predictors of Treatment Outcome Across the Three Medication Groups**

Interaction tests revealed that predictors of treatment outcomes were largely the same for all three medication groups. Indeed, no differential predictors were identified for the measures of retention and cocaine use, and only a few nonsignificant trends for medication group-specific predictors were identified on opiate use outcomes. These trends were observed between four predictors and opiate-related urinalysis results between the LAAM and buprenorphine groups. These trends suggested that being married and employed were both stronger predictors of fewer opiate-positive results in the LAAM group than in the buprenorphine group, suggesting that the presence of these two protective factors may be less relevant to achieving a positive treatment outcome in buprenorphine treatment than in LAAM treatment. Also, a trend emerged showing that a higher level of depression was a stronger predictor of fewer opiate-positive results in the buprenorphine condition than in the LAAM condition. This finding may suggest that depressed patients may benefit more from buprenorphine relative to LAAM treatment. The final interaction trend showed that having a greater number of months of alcohol use predicted a greater number of opiate-positive results in the LAAM condition than in the buprenorphine condition. This finding may suggest that having higher levels of alcohol use at the time of treatment intake may be less of a risk factor for a successful treatment outcome in buprenorphine treatment than in LAAM treatment.

One important finding was that no differential outcomes were observed for various subgroups of patients in methadone treatment compared with those in buprenorphine and LAAM treatments, suggesting that various subpopulations of opioid-dependent patients may have comparable success in treatment with buprenorphine or methadone. One possible reason for the lack of significant differences in predictors of outcome in methadone and buprenorphine treatments is that all participants in this study volunteered to accept treatment delivered in a traditional (for the U.S.) methadone clinic-like treatment setting. Specifically, participants attended a specially licensed, free-standing opioid maintenance specialty clinic, which required frequent visits with directly observed medication administration and urine collections. The present data indicate that the predictors of positive treatment outcomes in buprenorphine and methadone treatment do not differ in this methadone clinic-like context. One hope regarding the FDA’s recent approval of buprenorphine for use in medical office-based practice in the U.S. is that this new medication and new treatment context will attract new and possibly different types of opioid-dependent patients into treatment (Fudala et al., 2003). If future research identifies additional predictors of treatment outcome with buprenorphine in the office-based practice context, it might suggest that the predictors of treatment outcome are context-dependent and not medication-dependent. Such a finding, in turn, might argue for the value of similarly evaluating methadone in the office-based context as well.

As previously discussed, because of the exploratory nature of this study, we decided to examine both significant ($p \leq .05$) and nonsignificant ($p$ values of between .05 and .10) trends. Although conducting numerous statistical tests increases the likelihood of detecting effects due to chance factors alone, to the extent that the observed effects and
trends are consistent with relationships observed in other studies, these observations are likely not simply irrelevant, random-chance statistical anomalies. That is, a relationship is arguably not both a “statistical anomaly” and “already known.” As reviewed above, most of the observed relationships in the present study are consistent with what has been previously reported in the scientific literature, giving strength to our interpretation that the results are not due to chance. Also, despite the many statistical tests conducted and the examination of nonstatistical trends using a p value of .10 or less, few differential predictors across medication conditions were detected. Nonetheless, the results of this study should be interpreted in light of this methodological consideration.

This study offered the unique opportunity to evaluate whether different variables predicted outcome in methadone, LAAM, and buprenorphine treatments using data from a single-site, randomized controlled trial. Because such studies are not commonly or easily conducted, future research exploring these relationships may focus on the use of meta-analytic statistical techniques. Meta-analytic techniques enable a quantitative, aggregate analysis of results from multiple studies and thus a larger sample size, which enables identification and clarification of the nature of any relatively invariant underlying relations among data (Glass, McGaw, & Smith, 1981; Hunter & Schmidt, 1990). The present study identified several clinically important relations between patient baseline characteristics and treatment outcome. Nonetheless, the magnitude of these relationships was not always large. A meta-analysis of predictors of successful treatment outcomes with methadone, LAAM, and buprenorphine could aid in identifying the robustness of the relationships observed in the present study.

In summary, we believe that our study was the first to demonstrate that predictors of treatment success appear to be largely similar in LAAM, buprenorphine, and methadone treatment for opioid dependence. Our results did not reveal any factors that would strongly guide selection of one medication over the others. The outcomes of the study may be useful in deciding what ancillary services may be important to provide as part of such treatment depending on patients’ mental health or polydrug use problems.

References


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