Six-Month Trial of Bupropion With Contingency Management for Cocaine Dependence in a Methadone-Maintained Population

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Context: No effective pharmacotherapies exist for cocaine dependence, although contingency management (CM) has demonstrated efficacy.

Objective: To compare the efficacy of bupropion hydrochloride and CM for reducing cocaine use in methadone hydrochloride–maintained individuals.

Design: This 25-week, placebo-controlled, double-blind trial randomly assigned participants to 1 of 4 treatment conditions: CM and placebo (CMP), CM and 300 mg/d of bupropion hydrochloride (CMB), voucher control and placebo (VCP), or voucher control and bupropion (VCB).

Setting: Outpatient clinic at the Veterans Affairs Connecticut Healthcare System.

Participants: A total of 106 opiate-dependent, cocaine-abusing individuals.

Interventions: All study participants received methadone hydrochloride (range, 60-120 mg). Participants receiving bupropion hydrochloride were given 300 mg/d beginning at week 3. In the CM conditions, each urine sample negative for both opioids and cocaine resulted in a monetary-based voucher that increased for consecutively drug-free urine samples during weeks 1 to 13. Completion of abstinence-related activities also resulted in a voucher. During weeks 14 to 25, only completion of activities was reinforced in the CM group, regardless of sample results. The voucher control groups received vouchers for submitting urine samples, regardless of results, throughout the study.

Main Outcome Measure: Thrice-weekly urine toxicologic test results for cocaine and heroin.

Results: Groups did not differ in baseline characteristics or retention rates. Opiate use decreased significantly, with all treatment groups attaining equivalent amounts of opiate use at the end of the study. In the CMB group, the proportion of cocaine-positive samples significantly decreased during weeks 3 to 13 (P < .001) relative to week 3 and remained low during weeks 14 to 25. In the CMP group, cocaine use significantly increased during weeks 3 to 13 (P < .001) relative to week 3, but then cocaine use significantly decreased relative to the initial slope during weeks 14 to 25 (P < .001). In contrast, by treatment end, the VCB and VCP groups showed no significant improvement in cocaine use.

Conclusion: These findings suggest that combining CM with bupropion for the treatment of cocaine addiction may significantly improve outcomes relative to bupropion alone.

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Combined opioid and cocaine use is common, and up to half of patients undergoing methadone hydrochloride therapy abuse cocaine.1-3 The most common treatment for opioid dependence is methadone therapy, which decreases injection drug use and risk of human immunodeficiency virus infection and also improves social functioning.4,5 However, methadone does not directly affect cocaine use, with some studies6 even showing increases in cocaine use in patients undergoing methadone therapy. In a recent study, opioid-dependent patients who presented with both opioid- and cocaine-positive samples at baseline were almost 3 times more likely to drop out of treatment within a month compared with those who presented with only an initial opiate-positive result (17% vs 6%). At 1 month, samples negative for illicit drugs were noted in 3% of those with cocaine and opioid use at admission vs 43% of those with only an initially opioid-positive sample. Thus, cocaine use is related to poor outcome in patients undergoing methadone therapy.

Although methadone is an extremely effective treatment for opioid dependence, no similarly successful pharmaco-
logic intervention for cocaine abuse has yet been found. Therapeutic effects of antidepressants in cocaine-dependent patients have been examined in several trials, with mostly disappointing results. Nevertheless, compelling reasons exist to consider such agents. Although cocaine is a potent dopamine reuptake blocker, long-term use is associated with down-regulation of dopaminergic systems. Bupropion hydrochloride is a nor-

epinephrine and dopamine reuptake blocker. Consequently, by augmenting dopamine, bupropion may alleviate symptoms associated with this down-

regulation, leading to improved outcomes.

An initial test of the effectiveness of bupropion in cocaine-abusing patients undergoing methadone therapy was conducted by Margolin et al. This placebo-controlled double-blind study treated 149 patients for 12 weeks. Although no significant overall differences in cocaine use emerged between the bupropion and placebo groups, a significant effect of bupropion in lessening cocaine use occurred in a subset of depressed patients.

A form of treatment that is successful in reducing cocaine use in patients undergoing methadone therapy is contingency management (CM). Contingency management interventions provide reinforcement, typically in the form of vouchers exchangeable for retail goods and services, of objective evidence of positive behavior change. Often submission of drug-negative samples is rein-

forced, and in some studies, reinforcement is extended toward completion of specific activities related to long-term goal areas. Such procedures are hypothesized to improve overall functioning, thereby possibly extending beneficial effects even after reinforcement for negative samples is discontinued.

Contingency management interventions are usually considered an add-on to other forms of therapy, and growing evidence suggests that they may augment outcomes when combined with other effective therapies, including pharmacotherapies. In a study of desipramine hydrochloride paired with CM, for example, Kosten et al. found that the number of drug-free samples increased more rapidly in the desipramine and CM group than in those treated with either desipramine or CM alone. Additionally, the overall percentage of drug-free samples was significantly higher in the desipramine plus CM group (50%) than in the other treatment groups.

This finding of a synergistic effect of the combination of CM with an effective pharmacologic agent led us to evaluate the combination of bupropion and CM in treating cocaine-dependent patients undergoing methadone therapy in the present study. For the CM portion, we provided reinforcement contingent on both negative samples and activity completion for the first half of the study; in the second half of the study, reinforcement was provided only for activity completion. Hypotheses were that the combination of CM with bupropion would reduce cocaine use relative to either CM and placebo, placebo alone, or bupropion alone and that abstinence achieved during the initial reinforcement period would be maintained in CM patients even when reinforcement was no longer contingent on abstinence.

### METHODS

PARTICIPANTS

One hundred six individuals (mean ± SD age, 34.6 ± 9.01 years, including 30.2% females, 10.4% African Americans, 13.2% Hispanics, and 75.5% whites) seeking opioid maintenance treatment were recruited from the greater New Haven area (see Table 1). Each gave written informed consent, as approved by the Yale Human Investigations Committee and the Veterans Affairs Connecticut Human Studies Subcommittee. Each
individual must have met DSM-IV criteria for opioid dependence, have reported using opiates and cocaine in the week before study entry, and have had laboratory confirmation of opiate and cocaine use during the month before study entry. Exclusion criteria included the following: current diagnosis of alcohol or other drug physical dependence other than tobacco, opiates, and cocaine; history of schizophrenia or psychosis; any past seizure episode or history of anorexia nervosa or bulimia; current use of psychoactive medications; liver enzyme levels greater than 3 times the normal levels; and pregnancy or breastfeeding.

DESIGN AND PROCEDURE

This study was a 25-week, double-blind, placebo-controlled trial in which 106 individuals were randomized into 1 of 4 treatments: CM plus bupropion (CMB; n=27), CM plus placebo (CMP; n=25), voucher control plus bupropion (VCB; n=30), or voucher control plus placebo (VCP; n=24). The data manager conducted the randomization, which was computerized using an urn randomization technique, stratifying for sex, race, and age. Only the research pharmacist was aware of the medication condition. Research staff were aware of which patients were assigned to CM.

Patients attended the clinic at the West Haven Veterans Affairs Connecticut Healthcare System 6 days per week (Monday through Saturday) to complete study tasks, undergo counseling, and receive study medications. On Saturday, patients received study medication to take on Sunday. Patients in all conditions received once-weekly, individual cognitive behavioral therapy using materials from the collaborative cocaine psychotherapy study. For individuals receiving CM, counseling also included developing abstinence-related activities that were reinforced for completion.

ASSESSMENTS

At intake, each patient was interviewed using the Structured Clinical Interview for DSM-IV and Addiction Severity Index (5th edition). The Center for Epidemiological Studies Depression Scale (CES-D) was administered monthly. Primary outcome measures were the results of thrice-weekly cocaine and opiate urine toxicologic screening. Samples were obtained on Mondays, Wednesdays, and Fridays. Each sample was immediately tested on site using the BMS Fastest II Drug Screen Dipstick Test (Branan Medical Corp, Irvine, Calif), with a cutoff concentration of 300 ng/mL. In addition to thrice-weekly on-site tests, quality control samples were also sent to the Veterans Affairs hospital laboratory on Mondays for testing using an Olympus AU 640 Emit system (Olympus America Inc, Melville, NY). Samples were rated positive if the quantity of metabolite was greater than 300 ng/mL. The results obtained from the dipsticks and the samples analyzed by the Veterans Affairs hospital laboratory showed 100% agreement.

CM CONDITIONS

Study participants randomized to CM (with or without active bupropion) received vouchers for submitting urine samples negative for both cocaine and opioids. Initially, participants could earn $3 per negative sample. This amount was increased by $1 for each consecutive negative sample to a maximum of $15 per sample ($15 × 3 samples = $45 maximum per week). Any sample positive for opioids or cocaine or any missed sample reset the voucher amount to $3 for the next negative sample. Reinforcement for negative samples was provided during weeks 1 to 13. Participants who submitted all 36 negative samples could earn up to $462. Beginning in week 13, samples continued to be collected thrice weekly, but no vouchers were provided based on the results.

In addition to providing vouchers for submitting drug-negative samples, reinforcement was given for completing abstinence-related activities agreed on during weekly counseling sessions. Activities were designed to be incremental steps that would help the participant remain abstinent and included such items as “attend an Alcoholics Anonymous meeting” or “meet with staff regarding graduate equivalency diploma classes.” Only activities that were associated with an objective measure of verification (eg, signed slip from Alcoholics Anonymous chair, informational brochure, or receipt) could be selected. Although several weekly activities could be generated, a maximum of 2 activities per week were reinforced. Initial reinforcement per attained activity was $3, and this amount increased by $1 for each consecutively attained goal to a maximum of $10 per activity (2 activities × $10 = $20 per week). If an activity was not completed or verification was not provided, the voucher amount for the next activity was reset to $3. Participants in the CM groups continued to receive reinforcement for abstinence-related activities throughout the 25-week study, even after reinforcement was halted in week 14 for urine toxicologic screening results. In total, if all possible activities were completed across the 25 weeks, participants could earn up to $472 in vouchers. This amount of vouchers was in addition to any vouchers they may have earned for providing negative samples.

Once earned, voucher amounts awarded were never removed. Vouchers could be used for almost any item participants requested, although research staff retained the right to refuse to purchase certain items (eg, weapons or cigarettes). Typically, participants exchanged vouchers for gift cards to local stores, which were kept on site at the clinic for immediate access. When other requests were made, staff made every attempt to purchase and provide items by the next visit.

VC CONDITIONS

Participants randomized to VC conditions received $3 in vouchers per sample submitted, regardless of results. The VC participants received an additional $1 per week if they submitted all 3 samples each week (a maximum of $10 per week was possible, for a total of $250 if all 75 samples were submitted throughout the 25-week study). In the VC conditions, weekly goal-directed activities were not set during the cognitive behavior therapy sessions, and participants received no reinforcement related to counseling. Vouchers could be exchanged for retail goods and services similarly to the CM condition.

MEDICATIONS

Participants received methadone daily, 7 days per week. Methadone was dispensed in liquid form from a computer-controlled dispensing pump and ingested at the dispensing window under the observation of a nurse (except on Sundays, for which take-home doses were provided). Participants began receiving methadone during week 1. An initial dose of 30 mg was raised to a target dose of 60 mg by the end of week 1. Participants not adequately maintained on this dose were given adjustments based on a clinical assessment (range, 60-120 mg). Participants received methadone throughout the 25-week study.

Bupropion hydrochloride (sustained release) was initiated in week 2 for those assigned to the active medication condition. An initial dose of 75 mg/d was increased by 75 mg every other day, attaining a target dose of 300 mg by the end of week 2, which was continued for 25 weeks. Bupropion (or placebo) was given...
twice daily. At the time of methadone dispensing, each participant would ingest 200 mg of bupropion hydrochloride or a placebo pill. Both the bupropion and placebo tablets were further encapsulated at the Veterans Affairs pharmacy to appear identical. The dispensing nurse checked each participant’s mouth to ensure that the medication was taken. Each participant was given a 100-mg pill of bupropion hydrochloride or placebo to take home for ingestion 8 hours after the morning dose.

DATA ANALYSIS

Baseline characteristics of participants randomized to the 4 conditions were compared using $\chi^2$ tests for categorical variables and a general linear model analysis of variance for age. Baseline differences in CES-D scores were evaluated using a nonparametric Kruskal-Wallis test because of heterogeneity of variances. Retention across groups was evaluated using Kaplan-Meier survival analysis.

Urinalysis toxicologic screening and CES-D results collected over time were analyzed using hierarchical linear modeling (HLM). Statistical analyses using HLM have distinct advantages over standard regression analyses that make assumptions that observations across time are independent, measured at the same interval, have the same variance at each time point, and possess no missing observations. Analyses using HLM make fewer unrealistic assumptions regarding the nature of the data and allow for correlated observations, varying intervals among measurements, unequal variances, and missing data.

For the purpose of analysis, opiate and cocaine results were coded separately, and dichotomous results (negative or positive) were analyzed longitudinally. Across the 25-week study, there were 75 longitudinal toxicologic data points for both opiates and cocaine. An HLM modeling program for ordinal outcomes was used. In MIXOR, estimates derived from the analysis are expressed as logits, much as with logistic regression, and comparisons between models can be evaluated using overall log-likelihood statistics. All available data were used in the analyses, with no attempt made to interpolate missing data. Analyses using HLM fit a regression line for each participant, effectively interpolating missing data before deriving final estimates. Overall, including the 41.5% of participants who dropped out of treatment during the 6-month study, 21% of the 75 urine toxicologic screening results were missing, with no significant differences across groups in terms of missing data for either opiates or cocaine ($F = 0.59; P = .62$).

Methadone dosage began in week 1, and bupropion hydrochloride dosage began in week 2, reaching the target dose of 300 mg at the end of week 2. To reflect the timing of the full target doses, our analysis of opiate and cocaine results used data from weeks 3 to 25 only. Given that the contingencies for CM changed in week 14, a second HLM analysis using a piecewise method was conducted. Piecewise regression models are broken-line models in which the slope of the regression line may change at predetermined points called knots or breakpoints. A piecewise regression model provides parameter estimates for initial line slopes and for any change in slope for the regression segments that occur after the knot. The knot was set at week 14 to evaluate any change in toxicologic screening results for the second half of the study compared with the first half. Thus, the piecewise analysis allowed us to evaluate the change in slopes during weeks 3 to 13 for each group, differences in slopes among groups, and any changes in those slopes beginning in week 14. Of interest is whether the CMB combination shows a significantly improved slope over time vs the other groups.

RESULTS

DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Table 1 presents demographics and selected Structured Clinical Interview for DSM-IV diagnoses at intake. None of the conditions differed in terms of sex, race, age, or diagnosis of alcohol or cocaine dependence or major depressive disorder. No significant differences occurred at intake on the Addiction Severity Index number of days of self-reported heroin or cocaine use or Addiction Severity Index drug composite scores.

RETENTION

Figure 1 shows the proportion of participants retained per week by condition. No differences in retention occurred across the 25 weeks of the study (Kaplan-Meier log-rank test $= 0.34; P = .95$), with 60% of CMP, 56% of CMB, 63% of VCP, and 56% of VCB participants completing the trial.

CENTER FOR EPIDEMIOLOGIC STUDIES–DEPRESSION SCALE

Table 1 presents total intake CES-D scores for each group (overall mean ± SD intake score, 15.25 ± 12.76). No significant baseline differences occurred in CES-D scores using a GLM analysis of variance. The HLM analysis of the monthly total CES-D scores shows an overall significant reduction in scores throughout 25 weeks ($z = -5.4; P < .001$), with no significant differences by group (CMP vs CMB: $P = .93$; CMB vs VCB: $P = .51$; CMP vs VCP: $P = .95$; CMP vs VCB: $P = .56$; CMP vs VCP: $P = .88$; and VCB vs VCP: $P = .47$).

CM AMOUNTS

Table 2 presents voucher amounts earned by condition for each segment of the study. No differences occurred between the CMP and CMB groups in the overall amount of money earned from counseling activities (mean...
A repeated-measures analysis of variance that compared amounts earned for counseling activities between the first half of the study and the second half in the CMP and CMB groups found no differences for group by time (F = 0.21; \( P = .65 \)).

**Table 2. Amount Earned for Urine Results and Counseling Activities**

<table>
<thead>
<tr>
<th>Treatment Condition</th>
<th>Amount Earned for Urine Results, $</th>
<th>Amount Earned in Counseling, $</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Weeks 1-13</td>
<td>Weeks 14-25</td>
</tr>
<tr>
<td>CMP</td>
<td>65.32 (123.99)</td>
<td>71.80 (65.37)</td>
</tr>
<tr>
<td>CMB</td>
<td>116.22 (157.90)</td>
<td>83.48 (76.43)</td>
</tr>
<tr>
<td>VCP</td>
<td>103.42 (33.17)</td>
<td>107.21 (39.09)</td>
</tr>
<tr>
<td>VCB</td>
<td>112.57 (19.62)</td>
<td>95.23 (36.95)</td>
</tr>
</tbody>
</table>

Abbreviations: CMB, contingency management and bupropion hydrochloride; CMP, contingency management and placebo; VCB, voucher control and bupropion; VCP, voucher control and placebo.

*Data are presented as mean (SD). A repeated-measures analysis of variance comparing amounts earned for counseling activities between the first half of the study and the second half in the CMP and CMB groups found no differences for group by time (F = 0.21; \( P = .65 \)).

**COMBINED URINE RESULTS**

**Figure 2** shows the mean observed combined probability of either an opiate- or cocaine-positive sample across the 6-month trial. Data analyzed separately for opiates and cocaine indicated a differential response to condition based on type of drug. Consequently, we analyzed opiate and cocaine use separately.

**OPIATES**

**Figure 3** shows mean observed probability of an opiate-positive sample during the 6 months. Using MIXOR, 2 models evaluated individual sample results across weeks 3 to 25 (69 results total). The first fit a linear model to the data. The second used a piecewise analysis to model differences in opiate-positive results for weeks 3 to 13 vs weeks 14 to 25. The derived model log-likelihood statistics indicated that the piecewise analysis was a significantly better fit than the linear model (log likelihood = -2447.03 vs -2438.33; \( \chi^2 = 17.39; P = .002 \)).

**Table 3** presents a summary of the piecewise regression results. As expected for patients receiving methadone treatment, statistically significant reductions oc-
curred in opiate-positive samples over time in all groups during weeks 3 to 13. No significant differences occurred between groups in the rate of this decrease, with the exception that the CMB-treated participants decreased at a significantly lower rate than CMP (P < .001), VCP (P < .001), or VCB participants (P < .001). During weeks 14 to 25, the slope for the CMB group remained constant and did not change significantly (P = .95). In contrast, slopes for all other groups significantly increased, with the CMP group becoming slightly positive (slope, 0.001). These results indicate that all groups decreased opiate use during the first half of the study and that the rate of decrease leveled off during weeks 14 to 25. The CMB group was the only exception, maintaining a constant linear decrease across weeks 3 to 25. The HLM MIXOR analysis of the end point results, which were collapsed across weeks 24 and 25, indicates no significant differences among groups in the probability of an opiate-positive sample. These results are consistent with successful methadone treatment, in which one would expect rapid decreases in opiate use that taper off after stabilization.

Figure 3. Observed probability of an opiate-positive urine sample during weeks 3 to 25. Data shown are for the 75 individual urine samples across weeks 1 to 25. Only the first result of each week is labeled for clarity. A hierarchical linear modeling analysis was conducted on the individual results for weeks 3 to 25.

COCOAINE

Figure 4 shows the maximum number of consecutive weeks of continued opioid abstinence. The mean number of consecutive weeks was as follows: VCP, 3.4; CMP, 4.6; VCB, 5.5; and CMB, 5.7. The HLM Poisson analysis indicates that participants in the VCP group attained significantly fewer consecutive weeks of opioid abstinence compared with the other groups (CMB vs VCP: P < .001; VCB vs VCP: P < .001; CMP vs VCP: P = .03).

Figure 5 shows the mean observed probability of a positive cocaine sample. Two MIXOR HLM analyses were conducted, with the first fitting a linear model to the cocaine data. As with the opiate data, a second piecewise analysis modeled differences in cocaine-positive samples for weeks 3 to 13 vs weeks 14 to 25. The model log-likelihood statistics for the piecewise analysis indicate that it was a significantly better fit (log likelihood = −2125.46 vs −2144.44; χ² = 37.95; P < .001) than the linear model. Consequently, results are presented using this piecewise regression method, with week 14 being the knot.

Table 4 presents HLM results of this model. During weeks 3 to 13, CMB patients significantly reduced cocaine-positive samples relative to week 3. Gains made during weeks 3 to 13 were largely maintained during weeks 14...
...with a small but significant (P<.001) increase in slope during weeks 14 to 25. This positive slope is very slight (0.006). In comparison, CMP patients began to have a significant increase in the number of cocaine-positive samples during weeks 3 to 13 relative to week 3, after an initial decrease during weeks 1 and 2. However, during weeks 14 to 25, CMP patients evidenced a significant reduction in the number of cocaine-positive samples relative to the slope obtained for weeks 3 to 13.

Data for the VC groups (Figure 5) show an initial reduction in the probability of a cocaine-positive sample followed by a steady increase in this probability throughout the rest of the study. For VCB patients, the HLM analysis models these data as a significant increase in the probability of a cocaine-positive result from weeks 3 to 14, with a significant increase in this probability in the second half of the study compared with the first half (P=.03). For VCP patients, HLM models an initial reduction in the probability of a cocaine-positive result across weeks 3 to 13. However, in weeks 14 to 25, VCP patients showed a highly significant shift in slope, indicating an increasing probability of a cocaine-positive result (P<.001). By the end of the study, patients in both VC groups were showing similarly high levels of cocaine use.

To illustrate these group differences at the end of the trial, an HLM Poisson analysis evaluated cocaine results from weeks 24 to 25. The observed probability of a cocaine-positive sample was as follows: CMB, 0.33; CMP, 0.57; VCB, 0.66; and VCP, 0.74. The CMP group had significantly fewer positive results than all other groups (P<.001 for all). The CMP group had fewer positive results than the VCP group (P=.03), but VC groups did not differ (P=.25).

Figure 6 shows the maximum number of weeks of consecutive cocaine abstinence. The mean consecutive weeks of abstinence were as follows: VCP, 3.04; VCB, 4.90; CMP, 4.3; and CMB, 6.7. The HLM Poisson analysis results indicate that participants in the CMB group attained significantly more consecutive weeks of abstinence than all other groups (CMB vs CMP: P<.001; CMB vs VCP: P=.04; CMP vs VCP: P<.001). Conversely, VCP patients attained significantly fewer consecutive weeks of cocaine abstinence than the other groups (VCP vs VCB: P<.001; VCP vs CMP: P=.02; VCP vs CMB: P<.001). The CMP and VCP groups did not significantly differ.

**Table 3. Summary of Longitudinal Piecewise Hierarchical Linear Modeling Analysis of Effect of Treatment Group Condition on Probability of an Opiate-Positive Urine Sample**

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Slope Estimate</th>
<th>z Value</th>
<th>P Value</th>
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<tbody>
<tr>
<td>Weeks 3-13 (Urine Results 7-39)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMP</td>
<td>-0.04</td>
<td>-9.41</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>CMB</td>
<td>-0.01</td>
<td>-3.98</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>VCP</td>
<td>-0.04</td>
<td>-9.94</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>VCB</td>
<td>-0.04</td>
<td>-12.30</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Weeks 14-25 (Urine Results 48-75)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMP</td>
<td>0.001</td>
<td>5.88</td>
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</tr>
<tr>
<td>CMB</td>
<td>-0.01</td>
<td>-0.07</td>
<td>.95</td>
</tr>
<tr>
<td>VCP</td>
<td>-0.02</td>
<td>2.80</td>
<td>.005</td>
</tr>
<tr>
<td>VCB</td>
<td>-0.003</td>
<td>6.06</td>
<td>&lt;.001</td>
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Abbreviations: CMB, contingency management and bupropion hydrochloride; CMP, contingency management and placebo; VCB, voucher control and bupropion hydrochloride; VCP, voucher control and placebo.

*Model log-likelihood was -2438.33. The hierarchical linear modeling MIXPREG analysis (http://tigger.uic.edu/~hedeker/mix.html) results indicate the following: CMB vs VCP: P=.03; VCB vs VCP: P<.001; and CMP vs VCP: P<.001. All other comparisons are not statistically significant.

This study indicates that CMB is an effective treatment for cocaine abuse in methadone-maintained populations. This synergistic effect of medication and behavioral intervention is similar to that reported in the evaluation of desipramine combined with CM performed by Kosten et al. In the present study, CM alone was also effective in reducing cocaine use relative to the VCP condition, but only during the last half of the study.

The mechanism for the synergistic effect of CMB is not clear. One possible explanation is that bupropion may have been effective in helping participants obtain initial abstinence during the first 2 to 3 months of the study. This early abstinence would then allow participants in the CMB group to achieve reinforcement for this behavior. Participants in the CMB group, not having the benefits of bupropion, may not achieve reinforcement as early or as frequently, leading to decreased treatment response. Over time, cocaine use of CMP participants decreased as they begin to obtain sufficient reinforcement for abstinence. Participants in the VCB group may gain an early treatment benefit of bupropion on cocaine use coupled with a placebo response that is limited to only several months. In the absence of any powerful adjunctive treatment, such as CM, to build on this success, the initial gains related to bupropion may decline over time. However, developing a definitive explanation is diffi-
cult with the available data. In this study, the CM began immediately, whereas the bupropion did not reach the full dosage until week 3. Further clouding the issue are the early treatment gains made by all of the treatment groups, which may be linked to a generic placebo response and to effective methadone dosage. Stabilizing patients taking bupropion before initiating CM would help clarify this issue.

An early treatment benefit of bupropion may imply that the alleviation of cocaine withdrawal symptoms is related to its therapeutic action. Cocaine withdrawal symptoms include fatigue, psychomotor retardation, and hypersomnia. Bupropion enhances noradrenergic activity. By increasing noradrenergic activity, bupropion may alleviate some negative symptoms found in early cocaine withdrawal. This mechanism has also been proposed to explain bupropion’s effectiveness for smoking cessation. A study by Lerman et al found that change in negative affect was a significant mediator of bupropion’s effects on smoking cessation. Additionally, treatment with bupropion may abate impulsivity and increase concentration, perhaps leading to improved early treatment outcomes. Several studies have used bu-

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</tr>
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<tr>
<td>CMP</td>
<td>0.03</td>
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<td>CMB</td>
<td>−0.02</td>
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<td>0.02</td>
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<tr>
<td>CMB</td>
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<td>13.21</td>
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<tr>
<td>VCB</td>
<td>0.03</td>
<td>2.20</td>
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Abbreviations: CMB, contingency management and bupropion hydrochloride; CMP, contingency management and placebo; VCB, voucher control and bupropion; VCP, voucher control and placebo.

*Model log-likelihood was −2125.46. The hierarchical linear modeling analyses were conducted on 69 longitudinal dichotomous urine samples. Negative estimates indicate decreasing probability of a cocaine-positive urine sample. P values for weeks 3 to 13 reflect significant change across time for those weeks; P values for weeks 14 to 25 reflect a significant change in slope after week 13.
propion successfully in the treatment of attention-deficit/hyperactivity disorder, and more studies are necessary to further evaluate its efficacy in terms of treatment of cocaine dependence.

All 4 groups obtained significant reductions in depressive symptoms, with none of the treatments showing an advantage. This finding makes it unlikely that a reduction in depression is related to the early reduction of cocaine use in patients receiving bupropion.

Interestingly, ceasing reinforcement for urine results in the CM group halfway through the study did not alter the efficacy of the CM intervention. The CMB group maintained their early improvement in cocaine-free urine samples, whereas the CMP group decreased their number of cocaine-positive urine samples during the second half of the study. This result is consistent with other published works showing continued CM treatment effects even after changes in reinforcement from an escalating schedule to a fixed amount. The research in this regard is not completely consistent, however. Given this mixed result, more research is needed to definitively determine whether a reduction in voucher value has an impact on CM effectiveness.

Our study found that the CMB group had a slower rate of reduction of opioid use compared with the other treatment group, although all of the treatment groups showed similar rates of opioid use at the end of the study. Figure 3 indicates that this may be a statistical finding of little clinical significance. Because of the relative effectiveness of pharmacologic interventions, such as methadone for opioid dependence, there are few direct studies of the effectiveness of CM interventions on opioid use with which to compare this finding. One study that has examined this issue was conducted by Preston et al. That study evaluated the effects of (1) a CM intervention, (2) a methadone hydrochloride dose increment from 50 to 70 mg, (3) a combined CM and dose increase condition, and (4) neither intervention on heroin use in 120 patients enrolled in a methadone treatment program. They found that individually both CM and a dose increase were effective in reducing heroin use but that both together did not lead to larger reductions in opiate use. Our data are consistent with these findings. Following clinical examination, participants in our study were given dose increases for withdrawal symptoms or continued heroin use. Consequently, methadone dosage in our study was similar to the treatment practices of traditional methadone clinics and more effective than lower fixed maintenance doses, as used in the study by Preston et al. Higher methadone levels may lead to a ceiling effect in which CM shows little effect in individuals whose opiate dependence has been adequately addressed by methadone.

The findings of this study have several important implications for future research and treatment. In our study, CMB was superior in the treatment of cocaine use but not opioid use. This indicates that CM may not work for all substances of abuse, especially opioids, when the patient is already stabilized with methadone. Additionally, the findings of this study indicate that pharmacological agents previously dismissed as ineffective in a methadone-maintained cocaine-abusing population may in fact be effective when combined with the behavioral intervention of CM. Support for this position is derived from the study by Kosten et al, which found that a different agent, desipramine, combined with CM was an effective treatment for cocaine abuse in a buprenorphine hydrochloride-maintained population. Finally, our finding that CM remains effective even after a significant reduction in the amount of reinforcement has important practical implications for the use of this treatment in a clinical setting. Further research directed at reducing the cost of CM while maintaining its effectiveness will help to make this treatment increasingly feasible in mainstream clinical settings. One implication of this study is that, at least in methadone-maintained individuals who abuse cocaine, pharmaceutical augmentation of CM interventions may strengthen patient response, making less expensive reinforcement protocols possible.

Some limitations of this study must be acknowledged. Participants were given an evening dose of bupropion to take at home. This study did not use special bottle caps (Medication Event Monitoring System, Union City, Calif) or other methods to track participant compliance. To circumvent this issue, we gave two thirds (200-300 mg) of the daily dose at the methadone-dispensing window. Additionally, although we have hypothesized that the alleviation of cocaine withdrawal symptoms may be related to bupropion’s action, we did not measure these symptoms. Further studies should take into account both withdrawal symptoms and cognitive measures of attention and impulsivity.

This study indicates that bupropion augmented with CM may be an effective treatment for cocaine abuse. Further studies will help in delineating the exact mechanisms of bupropion’s effects and in addressing concerns regarding CM’s long-term efficacy and cost-effectiveness.

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