Published in final edited form as:
*Drug Alcohol Depend*. 2012 September 1; 125(1-2): 169–172. doi:10.1016/j.drugalcdep.2012.03.027.

# A Retrospective Analysis of Two Randomized Trials of Bupropion for Methamphetamine Dependence: Suggested Guidelines for Treatment Discontinuation/Augmentation

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## Abstract

**Background—**Two clinical trials have shown efficacy for bupropion in treating methamphetamine (MA) dependence among those with moderate baseline MA use. However, treatment response is highly variable and it is unclear what duration of treatment is necessary to determine if maintaining the treatment course is indicated or if discontinuation or augmentation is appropriate. The present study assessed the relationship among early bupropion treatment response for moderate MA users and end-of-treatment (EOT) abstinence. These data provide estimates of the duration of treatment and the degree of responsiveness required to persist in bupropion treatment.

**Methods—**Participants with moderate baseline MA use in the bupropion condition of two randomized double-blind placebo controlled trials were included. The relationship between early treatment response and EOT outcomes was assessed with Receiver Operating Characteristic (ROC) curves.

**Results—**With thrice weekly urine drug testing, excellent predictive power was established in the first two weeks of treatment. The inability to achieve at least three MA negative samples in the first two weeks is associated with greater than 90% likelihood of treatment failure. More closely approximating clinical settings, once-weekly testing featured reliable predictive power within three weeks, suggesting that the failure to produce at least two clean samples in the first three weekly visits confers high risk of treatment failure.

**Discussion—**The findings provide preliminary evidence to guide clinical decisions for moderate MA users receiving bupropion. The results are consistent with data from the smoking cessation literature and may highlight the importance of early response in addiction treatment.

### Keywords

methamphetamine dependence; abstinence; early response; bupropion; treatment switching



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**Conflicts of Interest** All authors declare no conflicts of interest.

**Contributors** Dr. Brensilver conceptualized the analysis, wrote the first draft of the manuscript and performed statistical analyses. Drs. Heinzerling and Swanson supervised all clinical and research activities of the Shoptaw (2008) trial. Drs. Shoptaw, Heinzerling and Swanson designed the Shoptaw (2008) trial. Drs. Heinzerling and Shoptaw edited the manuscript. All authors approved the final manuscript.

## 1. Introduction

Clinical response to pharmacotherapy for methamphetamine (MA) dependence is highly variable and no single medication has evidenced clear efficacy. Although not broadly efficacious for increasing the proportion of MA dependent participants achieving abstinence, bupropion has outperformed placebo among subgroups of MA users. Bupropion is approved as a treatment for depression, seasonal affective disorder and smoking cessation. It has several effects on the dopaminergic system that are relevant to the pathophysiology of addiction (Dwoskin et al., 2006; Rau et al., 2005). Two randomized placebo-controlled clinical trials have found that bupropion (300 mg/day), in conjunction with behavioral treatment, outperforms placebo in terms of MA-abstinence among those with more modest use during the weeks preceding treatment initiation (Elkashef et al., 2008; Shoptaw et al., 2008). A re-analysis of the Elkashef et al. (2008) trial using a nonbinary assessment of abstinence found beneficial effects for bupropion across the entire sample (McCann and Li, 2012). Despite preliminary evidence of efficacy at least in the subgroup of moderate users, treatment response is variable with the majority failing to achieve end-of-trial (EOT) abstinence.

A critical question for a clinician treating individuals with MA dependence is the duration of treatment necessary to determine if maintaining the treatment course is indicated or if discontinuation, adding an adjunctive treatment modality or recommending inpatient treatment is appropriate (Murphy et al., 2007). Quickly identifying likely treatment failures is valuable in improving clinical outcomes. Additionally, discontinuation of an ineffective medication may militate against disenchantment with treatment in general while conserving resources and minimizing needless medication exposure. Data for methamphetamine treatment is lacking but a substantial body of relevant research exists. Findings in clinical trials for smoking cessation and cocaine dependence are instructive. In her seminal paper, Kenford et al. (1994) found that pre-treatment variables generally failed to predict EOT and 6-month post-treatment smoking abstinence. However, abstinence in the second week of nicotine replacement therapy was strongly predictive of outcomes at 6 months, with two studies finding odds ratios between 4 and 24. Interestingly, few pretreatment variables were associated with early treatment abstinence and were only weakly predictive, suggesting that some unique information is captured by early treatment response. Plebani et al. (2009) assessed the predictive value of early abstinence for 407 cocaine dependent patients who received either putative medications or placebo. No medication effects were observed and analyses collapsed the medication and placebo groups. Abstinence during the first two weeks of treatment was related to EOT abstinence and to the proportion of cocaine-negative samples. The reader is directed to their paper for a fuller explanation of the relation between early and later abstinence in treatment for stimulant dependence.

While clinical experience suggests that early response is critical for methamphetamine treatment success, research has not addressed this question. The present study assesses the relationship among early bupropion treatment response among moderate users and EOT abstinence. This group was selected as there is preliminary evidence for the efficacy of bupropion with this subgroup and clinicians may rely on this medication in treatment settings. We examine the hypothesis that the first two weeks of treatment will provide adequate basis to predict likely treatment failures. While it is expected that some establishing early abstinence will relapse, we hypothesize that early response is critical for EOT abstinence.

## 2. Methods

### 2.1 Design

The data analyzed here are from two randomized, double-blind, placebo-controlled trials of bupropion. Participants received 150 mg of bupropion sustained release for the first three days and 300 mg (150 mg twice daily) thereafter. Methodological details are provided in the original reports (Elkashef et al., 2008; Shoptaw et al., 2008). Participants had current MA dependence verified by the Structured Clinical Interview for DSM-IV and featured no current dependence on other drugs of abuse. Individuals with serious medical or psychiatric disorders were excluded. A two-week non-treatment screening period was followed by 12 weeks of active treatment. All participants received cognitive behavioral therapy (CBT). Urine samples were collected thrice weekly and analyzed using radioimmunoassay. Some methodological differences existed between the trials. Shoptaw et al. (2008) provided weekly CBT and abstinence-based contingency management with a maximum earning potential of $537. Elkashef et al. (2008) provided thrice weekly CBT and attendance-based contingency management with a maximum earning potential of $530. Elkashef et al. (2008) verified positive radioimmunoassay results with gas chromatography/mass spectrometry and considered a sample negative if the assay was less than 300ng/ml and Shoptaw et al. (2008) relied on the qualitative radioimmunoassay results. All research activities were approved by the respective Institutional Review Boards. The current report selected moderate users as defined in the original reports (fewer than 19 self-reported days of MA use in the month before study initiation) who were receiving bupropion (N=55). The 55 participants included in the present analyses represent 48% of the combined sample who received bupropion.

### 2.2 Data Analysis

EOT abstinence was defined as no positive MA samples in the final two weeks of treatment with only one missing sample permitted per week. Participants with a single MA positive sample or missing more than one sample per week were considered persistent users. ROC analysis determined the extent of drug use in the first two weeks of treatment that optimally predicted persistent drug use at EOT. In determining early treatment response, missing samples were considered positive. Thus, the number of MA positive urine drug samples served as the classification variable with the failure to achieve EOT abstinence as the reference variable. Two additional ROC analyses assessed the predictive accuracy of one week and three weeks of MA testing for EOT outcomes. The area under the curve (AUC) between the three ROC curves was compared to determine the extent to which predictive power increases with each additional week of data (DeLong et al., 1988). Hosmer and Lemeshow (2000) have offered the following guidelines for interpreting AUC: .70–.80 is acceptable discrimination, .80–.90 is excellent and AUCs in excess of .90 are outstanding. As clinical care often utilizes weekly assessments rather than the thrice-weekly assessments featured in these clinical trials, the predictive power of a single screening in each of the first three weeks was also assessed. Summary statistics including AUC, sensitivity, specificity and positive and negative predictive values characterized different dimensions of predictive validity. Analyses were conducted with Stata (StataCorp LP, College Station, TX).

## 3. Results

### 3.1 Baseline Demographics and Drug Use

Participants (N=55) had a mean age of 36.5 (SD=10.6), 25% were female, averaged 12.8 years of education and were predominantly Caucasian (62%), Hispanic (18%) and Asian (11%). The mean number of days of MA use in the month preceding study screening was 8 (SD=6). Twenty-eight participants (51%) submitted at least one sample in the final week of

treatment. Fourteen patients (26%) achieved abstinence in the final two weeks of treatment. All 55 participants are included in the analyses.

### 3.2 ROC Analyses with Thrice Weekly Urine Drug Samples

We identified empirically-derived standards for predicting EOT outcomes by estimating the number of positive MA samples that would optimally predict persistent EOT MA use. A ROC analysis using the number of MA positive samples in the first two weeks of treatment estimated the predictive power of early treatment response on EOT status. Table 1 displays the predictive accuracy of early response for EOT outcomes. Using the Youden (1950) index, three MA positive samples within the first two weeks of treatment optimally predicted persistent EOT MA use. As there were six samples during this period, this result suggests that the inability to achieve at least three MA *negative* samples is associated with greater than 90% likelihood of treatment failure.

As we were interested in determining the optimal timing for decisions regarding switching treatment modality or intensity, ROC analyses assessed the comparative predictive power of one, two and three weeks of urine drug testing. If an additional week of testing data does not add substantially to the prediction of EOT outcomes, treatment switching decisions could be made earlier, thereby improving retention and clinical outcomes. The AUC reflects the probability that a randomly selected MA user at EOT will have more MA positive samples during the test period than a randomly selected participant who obtained EOT abstinence. For week 1 (three samples), week 2 (six samples) and week 3 (nine samples), the AUCs were .723 (95% CI=.569–.867), .801 (95% CI=.675–.926), and .808 (95% CI=.689–.928), respectively, all of which are significantly better than a non-informative variable which has an AUC of 0.5. In pairwise comparisons of these three AUCs, data from the first two weeks outperformed data from only the first week of testing. However, the third week of testing did not add significantly to the predictive power of week 2 data for predicting EOT outcomes. Of note, by week 2, the AUC had reached the threshold traditionally considered excellent. Results using a parametric model were consistent with results from the traditional empirical approach. In order to assess if study moderated the outcome, we fit a ROC model with study as a covariate. Results suggested this was not the case, and a pairwise test of the AUCs from the two studies revealed no difference (Elkashef AUC=.850; Shoptaw AUC=.823). Additionally, the ROC curve for the placebo group was compared with the ROC curve for the bupropion group. Results indicated very similar characteristics for the two groups, highlighting the general importance of early responsiveness for EOT outcomes.

### 3.3 ROC Analyses with Once Weekly Urine Drug Samples

Next, the predictive power of only the first sample of each week was examined – a standard more closely approximating many clinical settings. For week 1, week 2 and week 3, the AUCs were .673 (95% CI=.537–.809), .696 (95% CI=.533–.859), and .775 (95% CI=.655–.896), respectively. Three weeks of testing data outperformed one week ($p<.05$), and was marginally more precise in predicting EOT outcomes than two weeks of testing data ($p=.06$). Analyses suggested that the failure to produce two clean samples in the first three weekly visits confers high risk of treatment failure (positive predictive value=88%). The ability to predict treatment successes was substantially less precise. Having all negative samples in the first three weeks was associated with a negative predictive value of 51 percent. Analyses with the first two weekly visits suggested that failure to produce at least one clean urine also represented high risk of treatment failure (positive predictive value=85%). Six weeks of weekly samples did not improve the prediction of EOT outcomes beyond three weeks of samples.

## 4. Discussion

This research provides preliminary guidance for treatment discontinuation or augmentation for moderate users of methamphetamine treated with bupropion. Early treatment responsiveness appears important for EOT outcomes among a subgroup of MA dependent individuals in whom the medication has demonstrated preliminary efficacy. This finding is consistent with findings from cigarette smoking (Kenford et al., 1994) and represents a novel finding within the MA literature. These data suggest that clinicians prescribing bupropion can confidently predict treatment failures within two weeks when doing thrice weekly drug testing. Weekly testing yields acceptable predictive power within three weeks. Notably, the ability to predict treatment failure was substantially more precise than the prediction of treatment successes, a fact partially reflecting the overall treatment failure rate. The absence of an early response better predicts treatment failure than the presence of an early response predicts treatment success. Clinically, the prediction of treatment failures is relevant and signals the need for a change in modality or intensity. Unfortunately, treatment options are limited but more intensive behavioral intervention, pharmacologic treatment of comorbid psychiatric symptoms or inpatient treatment might be indicated. The present study found that early responsiveness in the placebo treated participants was equally important as early response in bupropion treated participants. Early treatment responsiveness appears to be an important variable in cocaine treatment as well (Plebani et al., 2009). These results may signal the general importance of early response in addiction treatment.

These findings should be interpreted in light of the study limitations. Analyses combined data from two trials which used a very similar but not identical study design. Sample size was limited to 55. In the Shoptaw et al. (2008) study, bupropion outperformed placebo among those with moderate use during the screening period rather than those with moderate self-reported use in the past 30 days. The definition of EOT abstinence is a measure of both retention and MA abstinence as attriters are considered non-abstinent. Consequently, the association between achieving early MA abstinence and EOT success are likely influenced in part by retention effects.

Despite the aforementioned limitations, the study provides preliminary guidance for determining treatment discontinuation or augmentation with one of the very few medications to show signs of efficacy in methamphetamine dependence.

## Acknowledgments

The authors gratefully acknowledge NIDA's permission to use data from the Elkashef et al. (2008) clinical trial and thank the investigators who conducted the trial.

**Role of funding source** Funding for this study was provided by NIDA Grants P50 DA18185, T32 DA026400, N01-DA8804 and N01-DA8824; NIDA had no further role in study design, in the collection, analysis and interpretation of data, in the writing of the report or in the decision to submit the paper for publication.

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## Table 1

Predictive power of thrice weekly urine drug screens during first two weeks of treatment for persistent MA use at EOT*

| MA Positive Screens | SN | SP | PPV | NPV |
|---|---|---|---|---|
| >=6 | 29.3 | 100.0 | 1 | .32 |
| >=5 | 46.3 | 92.7 | .95 | .37 |
| >=4 | 61.0 | 78.6 | .90 | .40 |
| **>=3** | **75.6** | **71.4** | **.89** | **.49** |
| >=2 | 80.5 | 57.1 | .85 | .49 |
| >=1 | 93.7 | 42.9 | .83 | .69 |

* ROC analysis assessed number of MA positive/missing urine drug screens to predict MA use at EOT. **Bolded** is optimal Youden (1950) predictor; SN=sensitivity; SP=specificity; PPV=positive predictive value; NPV=negative predictive value.

## Table 2

Predictive Power of Three Weeks of Once Weekly Screening Data for persistent MA use at EOT*

| MA Positive Screens | SN | SP | PPV | NPV |
|---|---|---|---|---|
| >=3 | 36.6 | 100.0 | 1.0 | .36 |
| **>=2** | **70.7** | **71.4** | **.88** | **.46** |
| >=1 | 82.9 | 50.0 | .83 | .51 |

* ROC analysis assessed number of MA positive/missing urine drug screens to predict MA use at EOT. **Bolded** is optimal Youden (1950) predictor; SN=sensitivity; SP=specificity; PPV=positive predictive value; NPV=negative predictive value.