Bupropion for the Treatment of Methamphetamine Dependence

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Overview


- Introduction/rationale
- Study design
- Participants
- Data analysis
- Results
- Discussion
Methamphetamine

- Synthetic stimulant drug
- Mechanism of action: increases dopamine/NE
- T½: 12 hours
- Routes of administration: IV, smoking, intranasal, and oral
Epidemiology

- Significant public health problem: serious medical, social, and economic consequences
- 2nd most commonly abused drug worldwide
  - High rates in Asia, Australia, Scandinavia, US
Medications considered for Methamphetamine

<table>
<thead>
<tr>
<th>Negative Results</th>
<th>+/Under Consideration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imipramine</td>
<td>Bupropion</td>
</tr>
<tr>
<td>Desipramine</td>
<td>Modafinil</td>
</tr>
<tr>
<td>Tyrosine</td>
<td>Topiramate</td>
</tr>
<tr>
<td>Ondansetron</td>
<td>Disulfiram</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Lobeline</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>Gabapentin</td>
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<td>Sertraline</td>
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</table>
Rationale for Bupropion

- No FDA-approved pharmacological treatment for MA dependence
- Psychotherapeutic interventions remain the mainstay of treatment
- Bupropion (Wellbutrin SR/XL, Zyban) is FDA-approved for treatment of depression and nicotine dependence, also improves ADHD sx’s
- Mechanism of action: inhibits reuptake of NE and dopamine
- May help alleviate WD sx’s (mimic depression)
Rationale – cont’d

- Chronic MA use results in low dopaminergic tone
- Bupropion blocks DA transporter
- Bupropion pretreatment has been shown to protect against acute MA-induced decreases in DA uptake in rats (Kim et al., 2000) and decrease neurotoxic effects in rats (Marek et al., 1990)
- Phase I study: bupropion was safe when co-administered with MA (no increase in CV or behavioral effects), and attenuated some of subjective effects of MA (“high” and craving) (Newton et al., 2006)
- Some evidence in cocaine dependence (depressed subset)
Study Objectives

Objectives: To assess the efficacy and safety of bupropion in reducing methamphetamine use in subjects with methamphetamine dependence.

Hypotheses: Bupropion treatment, as compared to placebo, will be associated with increased weeks of abstinence as measured by urine analysis.

- Bupropion will be efficacious in subgroup with lower MA use
- Bupropion will be efficacious in reducing craving
- Bupropion could help reduce MA dependence in subjects with MDD and ADHD
Study Design

- Double-blind, placebo-controlled study; 5 sites
- 151 adults with methamphetamine dependence randomized to receive bupropion SR 150 bid vs. placebo
- Exclusion criteria: seizure disorder, serious medical illness, psychiatric disorder requiring medication, pregnancy, court mandate
- 12 week trial; 90-minute CBT and UDS 3x’s/wk
Study Schema

**Activity**

<table>
<thead>
<tr>
<th>Study Week</th>
<th>Activity</th>
<th>Randomization Strata</th>
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</thead>
</table>
| -4         | Screening/ Baseline Assessments (weeks -4 to 0) | • use w/in the 30 days prior to study  
• gender  
• diagnosis/severity of depression |
| 0          | Randomization                                 | Bupropion N = 75  
Placebo N = 75                                                                 |
| 12         | Double-blind treatment* & assessments (weeks 0 to 12) |                                                                                     |
| 16         | Follow-up                                     | Final follow-up at week 16                                                            |

*Double blind treatment consists of daily bupropion (days 1 – 3: 150 mg, days 4 – 81: 300 mg, days 82 – 84: 150 mg) or matching placebo. Each arm also receives thrice-weekly cognitive behavioral therapy.*
Assessments

- SCID (baseline)
- Timeline follow-back SUR
- AEs
- Concomitant meds
- Med compliance
- Urine Drug Screen (UDS)
- Brief Substance Craving Scale (BSCS) (weekly)
- Vital signs (weekly)
- HAM-D (biweekly)
- ASI-Lite (baseline and end of tx)
- Physical exam, ECG, labs (baseline and end of tx)
Outcome Measures

- **Primary**
  - % of participants who abstained from MA during each wk of treatment (via UDS)

- **Secondary**
  - Subgroup analyses for treatment effects on the primary outcome: 1. gender, 2. low vs. high levels of MA use, 3. low vs. high levels of depression (HAM-D) 4. ADHD dx
  - Quantitative MA in urine
  - Self-report of daily MA use (timeline follow-back)
  - Changes in addiction severity (ASI-Lite)
  - Changes in craving (BSCS)
  - Changes in depression (HAM-D)
Data Analysis

- Generalized estimating equations (GEE) to compare weekly proportion of participants with MA-free urine between treatment groups
- Primary outcome data fitted with nonlinear (logistic) mixed effect model (NLMM) to further test combined effect of balancing factors and correct for multiple comparisons
  - Adjusts for baseline differences while estimating subject-specific effects of treatment
Table 1. Baseline characteristics of randomized participants

<table>
<thead>
<tr>
<th></th>
<th>Bup N=79</th>
<th>Placebo N=72</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>36.2</td>
<td>35.7</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>50 (63%)</td>
<td>51 (71%)</td>
</tr>
<tr>
<td>Female</td>
<td>29 (37%)</td>
<td>21 (29%)</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White, not Hispanic</td>
<td>59 (75%)</td>
<td>53 (74%)</td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>5 (6%)</td>
<td>5 (7%)</td>
</tr>
<tr>
<td>African American or Black</td>
<td>2 (3%)</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Asian or Pacific Islander</td>
<td>11 (14%)</td>
<td>10 (14%)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td><strong>Years of education</strong></td>
<td>12.6</td>
<td>12.4</td>
</tr>
<tr>
<td><strong>Days of methamphetamine use in last 30 days</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;= 18</td>
<td>36 (46%)</td>
<td>35 (49%)</td>
</tr>
<tr>
<td>&gt; 18</td>
<td>43 (54%)</td>
<td>37 (51%)</td>
</tr>
<tr>
<td><strong>Lifetime years of methamphetamine use</strong></td>
<td>10.42 (7.59)*</td>
<td>9.97 (6.10)</td>
</tr>
<tr>
<td><strong>Route of lifetime methamphetamine use</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasal</td>
<td>15 (19%)</td>
<td>10 (14%)</td>
</tr>
<tr>
<td>Smoking</td>
<td>49 (62%)</td>
<td>49 (68%)</td>
</tr>
<tr>
<td>Injection</td>
<td>15 (19%)</td>
<td>13 (18%)</td>
</tr>
<tr>
<td><strong>Depression (HAM-D Total &gt; 12)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>64 (81%)</td>
<td>57 (79%)</td>
</tr>
<tr>
<td>Yes</td>
<td>15 (19%)</td>
<td>15 (21%)</td>
</tr>
</tbody>
</table>

*Standard Deviation
Results: primary outcome

Fig 2 Percentage of Patients with Methamphetamine-Free Urine Week-Bupropion

Observed group means vs GEE fitted lines

Percentage of patients with Methamphetamine-free urine wk

Study Week Elapsed Since Randomization

GEE fitted lines  Bupropion  Placebo

Group means  Bupropion  Placebo
Results: low severity MA users

Fig 7 Percentage of Patients with Methamphetamine-Free Urine Week-Baseline Low Meth Use

Observed group means vs GEE fitted lines

- Percentage of patients with Methamphetamine-free study wk
- Study Week Elapsed Since Randomization
- GEE fitted lines
- Bupropion
- Placebo

Group means
- Bupropion
- Placebo
Results: high level MA users

Fig 5 Percentage of Patients with Methamphetamine-Free Urine Week Baseline High Meth Use
Observed group means vs GEE fitted lines

Percentage of patients with Methamphetamine-free study wk

Study Week Elapsed Since Randomization

GEE fitted lines
Bupropion
Placebo

Group means
Bupropion
Placebo
Results: secondary measures

- **Comorbid ADHD**
  - Only 20 subjects w/ ADHD, not balanced
  - No change in primary outcome between groups

- **ASI**
  - No significant differences between groups

- **BSCS**
  - No significant differences in slopes over time

- **HAM-D**
  - No significant differences between groups
Study Limitations

- Imbalance between groups on presence of ADHD
- DSM-IV raters lacked training in inter-rater reliability
  - Only 15% prevalence ADHD found
Conclusions

- Analysis of primary outcome showed trend toward statistical significance favoring bupropion for MA-free weeks (GEE, p=0.09).
- Secondary outcomes favored bupropion.
- Bupropion showed a statistically significant effect for MA-free weeks in the low/moderate group (GEE, p=0.03).
- Bupropion showed a statistically significant effect for weekly methamphetamine-free weeks in males (GEE, p=0.04).
  - 2/3 female patients were in high-use subgroup.
- Results suggest that bupropion, in combination with behavioral group therapy, was effective for increasing the number of weeks of abstinence in participants with low-to-moderate MA dependence.
Phase 2 Trial of Bupropion for MA Dependence

- 12-week NIDA-funded multisite trial
- 150 MA-dependent subjects to be randomized to bupropion vs. placebo for 12 weeks
- Only subjects who report <=18 d MA use in past 30
- Strata: gender, depression, ADHD, clinical site
- Analysis of genetic variants involved in susceptibility for MA dependence and response to bupropion
- Primary outcome: proportion of subjects who achieve abstinence during last 2 weeks of med dosing period