

Dextroamphetamine for Cocaine-Dependence Treatment: A Double-Blind Randomized Clinical Trial

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A properly implemented agonist treatment regimen should improve retention and reduce illicit drug use. Cocaine-dependent subjects (N = 128) were enrolled in a 12-week randomized, double-blind, placebo-controlled trial. In the multistage dosing design, subjects initially received placebo (PBO) or 15 to 30 mg of dextroamphetamine sulfate, sustained-release capsules. At week 5, the dose doubled to 30 mg or 60 mg for active groups. Subjects attended the clinic twice a week, provided urine samples, obtained medication, and had one behavioral therapy session a week. Retention was best for the 15- to 30-mg group, whereas the proportion of benzoylecgonine-positive urine screens was, from lowest to highest, 30 to 60 mg, 15 to 30 mg, and PBO at study end. Dosing must be refined. The results provide support for additional examination of the agonist model in psychostimulant-dependence treatment. (J Clin Psychopharmacol 2001;21:522-526)

MANY INVESTIGATORS HAVE examined pharmacologic approaches to cocaine-dependence treatment, but no medication has proven uniquely effective.¹⁻¹³ Agonists have been effective for treatment of opioid and nicotine dependence but have had limited evaluation for stimulant abuse. The agonist approach typically involves delivery of a similar or the same agent in a preparation form that has a slower onset. Results with methadone, levo- α -acetyl-methadol (LAAM), or buprenorphine for opioid dependence, and nicotine preparations for nicotine dependence suggest that properly implemented agonist therapy could improve retention and reduce cocaine abuse or dependence.

Readily available agonists for stimulant dependence include methylphenidate and amphetamine analogs. Early reports with methylphenidate were equivocal.^{11, 12} There is no evidence that methylphenidate would enhance retention,^{13, 14} and a recent trial demonstrated no decrease in cocaine use¹⁵; however, there may be benefit when attention-deficit/hyperactivity disorder is a comorbid condition.¹⁶

To pursue the agonist approach, we initiated the trial reported here using sustained-release dextroamphetamine along with collateral cocaine-amphetamine interaction studies in the human laboratory. In the latter studies, dextroamphetamine pretreatment produced some diminution in cocaine responsiveness, and physiologic effects were subadditive.¹⁷ Charnaud and associates¹⁸ reported positive results in a description of a clinical population receiving dextroamphetamine for amphetamine dependence, and this article provides a parallel result for cocaine dependence.

This study was reviewed and approved by the Committee for the Protection of Human Subjects, Health Science Center, University of Texas-Houston.

Methods

Subjects

Informed consent and intake evaluations were completed for 128 cocaine-dependent subjects in good medical health without other psychiatric diagnoses (except nicotine dependence), as determined by Structured Clinical Interview for DSM-IV (SCID).¹⁹ No subject who was offered entry refused participation.

Design

Subjects were randomly assigned to receive placebo (PBO) or one of two active medication groups in this double-blind trial that monitored the sequence shown in Table 1. The incremental dosing design was selected to minimize side effects.

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TABLE 1. Two-stage incremental dosing study design and phases of randomized, double-blind, placebo-controlled dextroamphetamine clinical trial. This strategy was used to avoid side effects and maximize safety in this initial trial.

Phase:	Intake	Stabilization 1	Study 1	Stabilization 2	Study 2	Study End
Duration:	2 Days	10 Days	28 Days	7 Days	56 Days	7 Days
Groups						
Placebo	No drug	Placebo	Placebo	Placebo	Placebo	No drug
Dextroamphetamine	No drug	15 mg	15 mg	30 mg	30 mg	No drug
Dextroamphetamine	No drug	30 mg	30 mg	60 mg	60 mg	No drug

Psychosocial therapy

Manual-driven, cognitive-behavioral psychosocial therapy was provided in this study, as well as previous studies,^{10, 15, 20, 21} for 1 hour each week by master's-level therapists.

Medication

The dextroamphetamine sulfate sustained-release regimen was administered twice daily: once within 2 hours of awakening, and once 6 hours later. Capsules containing PBO or medication were identical and included a total daily dose of 100 mg of riboflavin. Medication Event Monitoring System (MEMS) (Apex, Union City, CA) bottles were used and contained two capsules in each bottle, every day. Dosing occurred in the clinic on the two visit days each week.

Measures and data analysis

SCID, Addiction Severity Index,²² Beck Depression Inventory (BDI), and drug history, along with a standard physical examination and history, tuberculosis and human immunodeficiency virus (HIV) testing, urine screens, and an electrocardiogram were conducted at intake. A Side Effects Questionnaire and the BDI were administered weekly. Urine samples were collected and tested twice a week.

Descriptive and univariate statistics were calculated for patient intake data to identify baseline group differences. Retention data were analyzed using a parametric survival analysis and final group completion rates were compared using a χ^2 test. Repeated-measures data were analyzed using a BMDP "5V" module (Statistical Solutions Inc, Dallas, TX) for unbalanced repeated-measures data. This method uses all observations, and subjects are not deleted unless they do not contribute data. The resulting χ^2 values were sample-size corrected and reported as F -test equivalents.²³

Results

The sample of 128 subjects was of 79% male, 58% black, 31% white, and 9% Hispanic. Thirty-eight percent of subjects were employed. The average age was 36 years (SD, 6.4), and years of education was 12.7 (SD, 1.9). Cocaine use at intake was crack or freebase (22%);

powder or snow (5.7%); other (0.8%); a combination of crack, powder, and speed (69.9%); or all forms mentioned above (1.6%). The reported frequency of use was "less than once a month" (2%), "less than once a week" (12.7%), "once a week" (14%), "several times a week" (48%), "once a day" (16.7%), and "greater than three times a day" (6.7%). There were no differences across groups on these variables ($p > 0.50$).

Retention

Seven subjects (of 128) did not have their dose doubled or their dose was reversed after doubling and retention was deemed finished at the point of protocol deviation. Study completion rates for PBO, 15 to 30 mg, and 30 to 60 mg groups were 22.9%, 40.4%, and 8.7%, respectively. The completion rate differences were significant (likelihood ratio [LR] $\chi^2 = 13.49$, $df = 2$, $p = 0.0012$, $N = 128$). Survival analysis of the study phase retention curves (Fig. 1), indicated retention differed by dose group from the beginning of the 13-week study phase, (LR $\chi^2 = 10.05$, $df = 2$, $p = 0.0066$, $N = 101$). Retention, from best to worst, was 15 to 30 mg, PBO, and 30 to 60 mg, respectively, with similar survival curve analysis results from beginning of medication (LR $\chi^2 = 16.28$, $df = 2$, $p = 0.0003$, $N = 128$). Separate analysis of retention, subsequent to the dose doubling at week 5

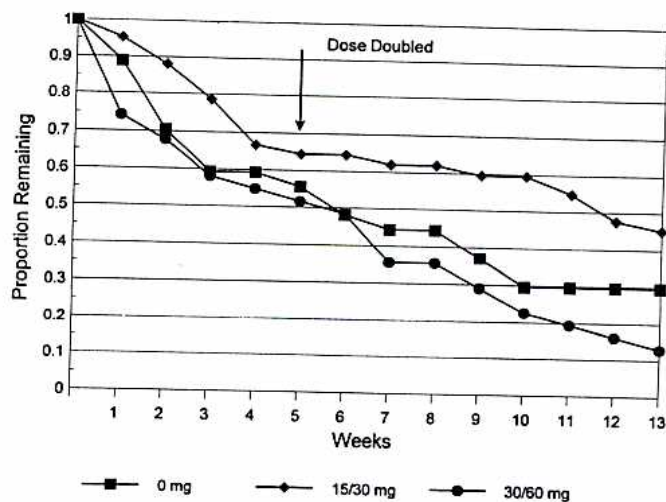


FIG. 1. Retention data from "Study Start" (excluding INT and Stab I periods), which includes only those subjects who completed the run-in period.

(based on patients who successfully started week 5), failed to detect reliable group differences.

Compliance

Amphetamine-positive urine screens throughout the study were 0%, 81.05%, and 82.05%, respectively, for 0 (PBO), 15/30, and 30/60 mg dose groups. Compliance measured by riboflavin fluorescence (cutoff <10) was 97.2%, 93.3%, and 93.0%, respectively, for the 0, 15/30, and 30/60 mg dose groups.

Dropouts and side effects

Six subjects stated medication side effects as reasons for dropping out. Differences in the frequency of side effects on the 33-item list collected each week were analyzed as a function of dose and time using maximum-likelihood repeated-measures variance for unbalanced data. Few items varied when intake values were used as covariates. Varying with increasing dose were sleeping less ($F = 4.91$, $df = 2,115$, $p = 0.009$, $N = 117$); fever ($F = 4.37$, $df = 2,115$, $p = 0.0148$, $N = 117$); mouth or tongue twitch ($F = 3.53$, $df = 2,114$, $p = 0.0325$, $N = 116$); and dizziness ($F = 2.85$, $df = 2,115$, $p = 0.062$, $N = 117$). Side effect frequencies, changing in an interactive pattern between dose and time were eating ($F = 3.39$, $df = 6,153$, $p = 0.0036$, $N = 117$) and muscle twitches or movements ($F = 2.16$, $df = 6,153$, $p = 0.0496$, $N = 116$).

Cocaine use

Urine screens were considered presumptive for cocaine if benzoylecgonine (BZ) levels were 300 ng/mL or greater. There was no difference in result, whether examined by a dichotomous positive/negative indicator or a creatinine-adjusted quantitative BZ measure. The proportion of urine screens that were positive at intake was 0.80, 0.68, and 0.65, respectively, for subjects randomly assigned to the 0, 15/30, and 30/60 mg groups. For the complete sample, differences were not significant (Pearson $\chi^2 = 2.257$, $df = 2$, $p = 0.323$, $N = 128$). Cocaine use during the stabilization phase did not differ by group ($F = 0.361$, $df = 2,111$, $p = 0.6975$, $N = 114$); however, all groups improved. The average number of cocaine-positive urine screens for the complete sample did not differ as a function of dose ($F = 0.147$, $df = 2.99$, $p = 0.864$, $N = 102$) during the initial dose during the dose-doubling period (last 2 months; $F = 0.71$, $df = 2.50$, $p = 0.497$, $N = 53$).

Intake BZ is predictive of outcome.^{10, 15} Here, invariably, intake cocaine-urine screen was a significant predictor of subsequent cocaine use: stabilization ($F = 19.96$, $df = 1,110$, $p < 0.0001$, $N = 114$); month 1 ($F = 14.86$, $df = 1.98$, $p = 0.0002$, $N = 102$); and after the dose-doubling ($F = 7.71$, $df = 1.49$, $p = 0.0077$, $N = 53$). Quantitative BZ data produced the same pattern with no dose-by-time effects. Post hoc analyses revealed 16 subjects

exhibited no positive screens from intake through study completion or dropout. When these subjects were removed from the data set, a different pattern of cocaine use appeared (Fig. 2). The data for month 1 were similar to those for the complete sample, but differences emerged after the dose was doubled (months 2 and 3). During the 8-week second phase, the 30-mg and PBO groups showed a trend in their difference ($F = 2.5$, $df = 1.29$, $p = 0.125$, $N = 31$). The 60-mg group showed fewer BZ-positive urine screens than the PBO group during month 3 ($F = 4.577$, $df = 1.9$, $p = 0.061$, $N = 11$). The probability values are not corrected for post hoc comparisons, and sample sizes are small but the data form a dose response consistent with a substitution hypothesis.

Systolic and diastolic pressures and heart rate were recorded at intake and weekly thereafter. The aggregated data, by study period, (intake/dosing/dose-doubling) were analyzed using a BMDP 5V module, a maximum likelihood analysis of repeated measures when data are missing. Separate analyses corresponded to each of these dependent measures, with intake measures as covariates (group-by-time repeated-measures analysis of covariance).

Subjects were generally normotensive with no differences across groups at intake. Mean systolic/diastolic pressures (standard error) across intake, phase 1, and phase 2 (dose-doubling) for PBO were 123 (-1.9)/78.2 (-1.2), 124.4 (-2.2)/78.9 (-1.7); and 127.7 (-2.4)/78.9 (-1.7); for 15 to 30 mg, 119 (-1.7)/78.4 (-1.2), 124.6 (-1.3)/78.8 (-0.9), and 127.4 (-1.9)/81.1 (-1.5); and for 30 to 60 mg, 121 (-2)/77.7(-1.3), 123.8 (-1.7)/77.7 (-1.3), and 124.8 (-2.2)/80 (-2.2). Heart rates (standard

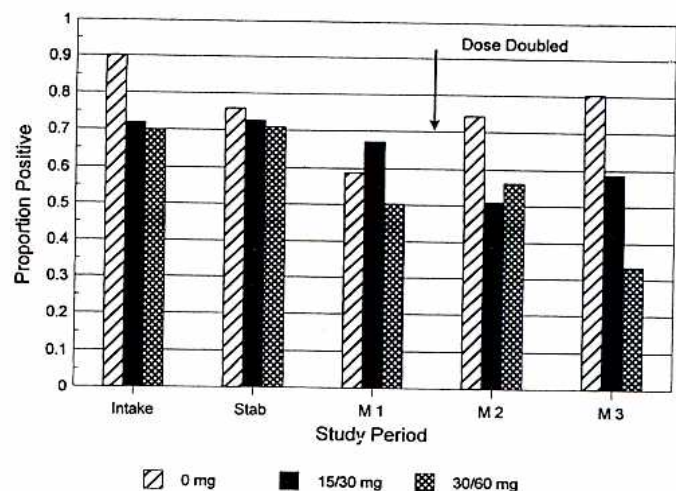


FIG. 2. The data presented are dichotomous (positive/negative), with a 300 ng/mL cutoff for the group with the 16 "nonusers" (equally distributed across groups—see text) who provided no BZ-positive screens from intake to end were removed. The arrow indicates the point at which the dose was doubled. Data for the dose-doubling week are not included in these analyses.

error) across intake, phase 1, and phase 2 (dose-doubling) for PBO were 75.4 (-1.8), 74.6 (-2), and 72.5 (-2.9); for 15 to 30 mg, 73.5 (-0.9), 78.4 (-1.3), and 80 (-1.3); and for 30 to 60 mg, 75.1 (-1.5), 79 (-1.5), and 80.7 (-4.6). Maximum likelihood analyses of systolic and diastolic blood pressure, respectively indicated a trend for the time variable ($F[1,48] = 3.2, p = 0.079$); ($F[1,48] = 3.8, p = 0.058$, respectively) with no other measures being statistically significant. There were no differences in dose-condition or dose-by-time interactions ($p > 0.30$). Main effects of dose ($F[2,116] = 3.96, p = 0.022$) and time ($F[1,46] = 5.3, p = 0.026$) were found for the heart rate. Heart rate increased 1.5 beats per minute, on average, for drug groups from single- to double-dosing.

Beck Depression Inventory

There were no significant BDI score differences across groups at intake ($F = 1.91, df = 2,125, p = 0.153, N = 128$). BDI scores declined during the first 4 weeks ($F = 5.47, df = 3,193, p = 0.0013, N = 93$) and evidenced a trend toward differing as a function of both condition and time ($F = 1.74, df = 6,184, p = 0.1141, N = 93$). Subjects in the group initially given a dose of 30 mg remained relatively stable and had higher BDI scores than the two other groups, whose values declined over weeks 1 to 4. Analysis of BDI scores, after dose-doubling, indicated a significant time effect ($F = 2.81, df = 7,273, p = 0.0076, N = 55$), with scores decreasing. However, a significant dose-by-time effect was also present ($F = 2.05, df = 14,252, p = 0.0151, N = 55$), with BDI scores declining for the 30/60 mg group, increasing for the 15/30 mg group, and remaining stable for the PBO group.

HIV

Of the 128 subjects who began study (received medication), 8 were HIV positive, and 1 was indeterminate, at intake and follow-up screening. No one tested from negative to positive during the study.

Discussion

This article describes the first randomly assigned, double-blind study examining an amphetamine analog as a prototype agonist for stimulant-dependence treatment. The results point to improved retention and reduction in illicit drug use, two predicted functions of agonist treatment. The optimal dose is likely between 30 and 60 mg for this preparation. The divergent response at different doses parallels other agonist literature; for example, the use of methadone varies as a function of dose,²⁰ clinical circumstances of its administration,²⁴ and other environmental factors.^{21, 25} The results support, and are supported by, an open clinical, dispensing report of Charnaud and associates¹⁸ in which dextroampheta-

mine immediate-release was administered to amphetamine-abusing patients.

The cause of the discrepancy between the two compliance measures is unknown. Riboflavin accumulation is known to occur in some individuals, whereas some may be more effective drug metabolizers, thus producing negative dextroamphetamine screens. Melding the dextroamphetamine-positive/PBO-negative and the riboflavin-positive rates suggests excellent compliance.

The study design was complex, but served well. Post hoc, it was clear that subject selection could be improved. The results were skewed by the subset of 16 subjects who had no positive screens at intake or during the study. We now only include subjects with two or more BZ-positive urine screens during stabilization. Optimal agonist dosing and benefit may be dependent on this characteristic.

Our clinical research center studies,¹⁷ as well as results in this trial, suggest that mood and cardiovascular effects are minimal, and that dextroamphetamine may diminish cocaine responsivity. The absence of adverse effects diminishes concerns; however, caution is essential. In summary, the data warrant pursuit of the model with careful attention to the two criteria, retention and decreased abuse.

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