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A Controlled Trial of Flumazenil and Gabapentin for Initial Treatment of Methylamphetamine Dependence

HAROLD C. URSCHEL III, MD, MMA; LARRY L. HANSELKA, PHD;

MICHAEL BARON, PHD

From Research Across America, CNS Research Group, Dallas, Texas (H.C.U and L.L.H); and The University of Texas at Dallas, Richardson, TX (M.B.).

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Reprint requests and correspondence to Harold C. Urschel III, MD, MMA, The Urschel Recovery Science Institute, 8222 Douglas Avenue, Suite 375, Dallas, TX 75225. (Urschel@recovery-science.com).

Abstract

Drug use has been associated with craving, which may be described as a powerful and sometimes overwhelming urge to use the drug. Patients seeking treatment for methylamphetamine dependence must cope with drug cravings as they engage in psychosocial treatments. Changes in brain $GABA_A$ receptors during substance use and withdrawal provide a neurobiological basis for craving and associated anxiety. Flumazenil (a benzodiazepine antagonist) plus gabapentin (an antiepileptic) were compared with placebo in a randomized, double-blind study to assess effects on craving during initial treatment for methylamphetamine dependence. Evaluation was conducted over a 30-day period. Craving and drug use were found to be highly correlated. Craving was significantly reduced in the flumazenil plus gabapentin group compared with placebo following the initial treatment period and throughout the 30 days. Decreased methylamphetamine use was also observed, as measured by urine drug screens and self-reports.

Keywords

Craving, methylamphetamine dependence, GABA receptors, flumazenil, gabapentin

Introduction

Craving, which may be described as a powerful and sometimes overwhelming urge to use, is an important concept in the substance dependence literature. Craving remains difficult to define, however, partly because it appears involve the interplay of behavioral, social, motivational and neuronal factors. These factors, and the resulting craving, produce neurobiological effects, even in the absence of acute drug administration. A measure of these effects is change in brain glucose metabolism, which is correlated with craving self-reports (Grant *et al*., 1996; Maas *et al*., 1998; Wexler *et al*., 2001). The level of glucose metabolism in the orbitofrontal cortex and striatum was proportional to craving intensity, where greater craving leads to higher metabolism (Goldstein and Volkow, 2002). The elevation of glucose metabolism with craving in certain brain regions, suggests that craving is associated with an increased neuronal excitation and activity.

The GABA-A receptor mediates most inhibition in the brain. The receptor is a pentamer, usually comprised of 2α, 2β and 1γ or δ subunit (Chang *et al*., 1996). The most abundantly expressed GABA-A receptor in the brain, from a pool of sub-types, is α1β2γ2, whereas α4-containing GABA-A receptors have normally very low expression. The plasticity of the α4-subunit to increase has been demonstrated with exposure to, and withdrawal from, substances of abuse (Smith *et al*., 2007a.; Biggio *et al*., 2007; Holt *et al*. 1996; Smith *et al.*, 2007b.) Increased expression of the α4 subunit of the GABA-A receptor can alter neuronal excitability, and the increased abundance of this subunit has been associated with increased anxiety (Smith *et al*., 1998; Gulinello *et al*., 2002; Cagetti *et al*., 2003; Olsen *et al*., 2005).

The dopamine system has historically been considered implicit in craving phenomena. Dopamine, released from mesocorticolimbic neurons, is considered to be a determinant in motivational aspects of stimuli (Hyman and Malenka, 2001). However, GABAergic inhibition of dopaminergic and other types of neurons that project to brain structures involved in emotional processing may contribute to reducing anxiety and craving (Nestler *et al*., 2001). Restoring GABA-gated current across the GABAergic system may attenuate craving. Neuronal pathways for both 'reward' craving, the desire for reward and/or stimulation (associated with dopaminergic/opioidergic dysregulation), and 'relief' craving, the desire for reducing tension and/or anxiety (associated with GABAergic dysregulation), may be considered dependent on GABA receptor function (Addolorato *et al*., 2005; Verhuel *et al*., 1999).

Flumazenil, a benzodiazepine receptor antagonist (Hunkeler *et al*., 1981), has been shown to prevent the increase in α4-subunit gene expression and associated change in GABA-A receptor function in models of exposure to substances of abuse (Biggio *et al*., 2007; Smith *et al*., 2007b.) Pre-clinical studies show that flumazenil, which acts as an agonist at α4 subunits, reduces withdrawal-induced anxiety-like behavior (File *et al*., 1989; Knapp *et al.,* 2004; Kapczinski *et al*., 1994), as well as alcohol dependence and tolerance (Buck *et al*., 1991).

Gabapentin is an antiepileptic that acts as a GABA agonist and is thought to decrease brain glutamate concentrations (Dougherty *et al*., 2001). Originally designed as a structural analog of GABA, gabapentin appears to have a different site of action than other antiepileptic drugs, and little affinity for GABA-A receptors. Since gabapentin does not bind to benzodiazepine receptors (Dougherty *et al*., 2001) its action in the

treatment of stimulant dependence may be complimentary to flumazenil. It has been reported to reduce craving (Myrick *et al*., 2001; Raby, 2000).

Craving has become a target in the treatment of substance dependence. Recent research has demonstrated a relationship between craving and subsequent substance use. Hartz *et al.* (2001), with a sample of methylamphetamine dependent patients in treatment, found that craving significantly predicted subsequent methylamphetamine use. The relationship between craving and cocaine use was studied by Weiss *et al.* (2003) within a NIDA Collaborative Treatment Study (Crits-Christoph *et al*., 1999). The investigators found that craving scores were a significant predictor of drug use during the following week and throughout treatment for cocaine dependence. Rohsenow *et al.* (2007) also concluded that urge/craving predicts early drug use and represents a valid treatment target.

Results of an earlier, prospective, open-label trial suggested that a combination of flumazenil and gabapentin could reduce cravings in individuals with methylamphetamine dependence (Urschel *et al*., 2007). A medical treatment that can reduce cravings may improve patients' ability to become more fully engaged and involved in psychosocial treatment, which is essential to the recovery process, especially during the initial stages of treatment. The present study was designed to confirm the earlier findings in a double-blind, placebo-controlled trial. The investigators hypothesized that treatment with flumazenil and gabapentin would significantly decrease craving during initial treatment for methylamphetamine dependence.

Materials and Methods

Participants

Of the 181 persons screened for the study, 135 men and non-pregnant, non-lactating women ages 18-55 were randomized to either the active treatment group (N=68) or placebo group (N=67). All participants had a diagnosis of methylamphetamine dependence based on the *Diagnostic and Statistical Manual of Mental Disorder, Fourth Edition, Text Revision;* had used the drug within 3 days of receiving the treatment; desired to stop using methylamphetamine; were able to participate in the study for 30 days; provided an observed urine specimen that was negative for benzodiazepines; and had given permission to contact persons who knew their whereabouts for tracking purposes. Persons were not eligible for the study if they had a diagnosis of alcohol or non-methylamphetamine dependence (except nicotine); a full-scale IQ equivalent score < 80 or a blood alcohol level > .08 mg%; recent evidence (≤2 years) of cardiac ischemia or myocardial infarction; renal, hepatic, or gastric disease, uncontrolled hypertension, advanced HIV disease, or other medical or psychiatric condition that might preclude safe participation in the study; recently participated in a clinical trial of an investigational medication; and used benzodiazepines within 14 days of the study.

During screening of each potential participant, informed consent was obtained, a complete psychiatric evaluation and medical and physical evaluations were conducted, a laboratory panel (complete blood cell count, chemistry panel, liver function test, thyroid-stimulating hormone blood test, serum human chorionic gonadotropin test in women of child bearing potential, electrocardiography, urinalysis, and urine drug screen [UDS])

was performed, and any history of methylamphetamine or other drug use was elicited. Pretreatment information included participant demographics, a detailed history of methylamphetamine use during the past 30 days obtained using the timeline followback (TLFB) method, cognitive status as measured by the Shipley Institute of Living Scale (SILS), and methylamphetamine craving scale.

Study Design and Treatments

This was a 30-day, randomized, double-blind, placebo-controlled, parallel-group study. Following screening and baseline assessment, 135 eligible participants were randomized to either (1) an active treatment group receiving flumazenil, 2 mg administered IV on days 1, 2, 3, 21, 22; oral gabapentin up to 1200 mg/day, and hydroxyzine 50 mg for pre-infusion and PRN for sleep; or (2) a control group receiving inactive formulations of the medications. Participants returned on Days 6, 13, 20, and 30 for observed urine drug screen (UDS) samples, self-report of drug use, adverse events assessment, and drug craving measures. They also returned on Day 4 to have a UDS. Eighty-eight subjects, 44 in each group, received all 5 flumazenil infusions and completed the day 30 data collection visit. All participants received drug abuse counseling and nutritional support. To encourage adherence to protocol, participants received incentives if they completed their appointed visits ±1 day ($50 voucher for food or gasoline).

The study was conducted by the CNS Research Group at Research Across America, an outpatient clinical research facility in Dallas, Texas. Study procedures,

consent form, and media advertising were approved by the Western Institutional Review Board. The study was conducted from January 2007 to October 2007.

The medications used in the pharmacologic portion of the program—flumazenil (a benzodiazepine antagonist) and gabapentin (an anticonvulsant)—were administered using a sequential-dosing algorithm. The medications are all FDA approved for uses other than drug dependence and were purchased by the researchers from pharmaceutical sources.

Once enrolled in the study, participants were treated for 3 consecutive days with either the medications or placebo, depending on randomized group assignment. Participants in the placebo group received inactive formulations of the medications: infusions of normal saline instead of flumazenil, and identical capsules containing fructose instead of gabapentin (300 mg).

The flumazenil (or placebo) was administered over 30 minutes by incremental IV bolus through an intravenous line kept open with Ringer's Lactate Solution. Flumazenil was administered in incremental doses of 0.1 mg to 0.3 mg over 30 minutes. Gabapentin up to 1200 mg/day, in a titrated dose schedule for was self-administered once daily.

Three weeks after the initial flumazenil infusion (days 21 and 22), participants in both groups returned to the clinic for "booster" infusions (identical to those given previously) administered over 2 consecutive days. At the weekly data collection visits, all participants provided a urine sample and met with a therapist for psychosocial treatment. The treatment was based on the Matrix™ Model, a manualized intervention incorporating cognitive-behavioral and psychoeducational strategies.

Assessments

Methylamphetamine Craving

Craving data were collected using 6 visual-analogue scales and 4 categorical scales. Subjects were asked to rate along a 10-point scale their most intense craving during the past week, frequency of urges to use, strength of desire right now, strength of desire during last 24 hours, strength of desire when reminded, and likelihood of using again. A composite craving score was derived by combining the 6 visual-analogue scales. The categorical scales assessed time occupied by thoughts, frequency of thoughts, disturbance by thoughts, and effort made during the week to keep from using methylamphetamine. The craving scales were used to assess change in self-reported cravings for methylamphetamine from baseline (screening) to the end of the 30-day trial. The scales were administered at screening and at days 6, 13, 20, and 30 of the study.

Methylamphetamine Use

Methylamphetamine and other drug use were monitored over a 30-day period. The timeline followback (TLFB) method was used to obtain retrospective estimates of participants' daily substance use. Participants were given a calendar as a memory aid and asked to note on the calendar events and activities associated with drug use on a day-by-day basis. Other memory aids were used by the interviewer to enhance recall. The TLFB was administered at screening (covering the previous 30 days) and at study visits on days 6, 13, 20 and 30.

Urine drug screen (UDS) results were used as an index of methylamphetamine use and to assess the validity of self-reports of methylamphetamine and other drug use. The Redwood Urine Narcotic Screening Panel-Dip Device (Redwood Toxicology, Santa Clara, CA), a multipanel 10-test UDS, was used to detect the presence of drugs and/or drug metabolites in subjects' urine. The Panel-Dip Device is a one-step lateral flow chromatographic immunoassay with test strips. Test strip results were not confirmed through independent lab analyses. Observed UDS were collected at baseline (screening) and at each study visit throughout the duration of the 30-day trial.

Participant Characteristics

There were 135 participants in the study, of which 68 were randomized to active (flumazenil, gabapentin, hydroxyzine) treatment and 67 to placebo treatment. Eighty-eight patients, 44 in each group, received all five infusions, either saline or medication, and attended the day 30 visit (65.2%).

Participant disposition regarding time to discontinuation is presented in Figure 1. There were no significant differences between groups with respect to discontinuation from the trial.

Figure 1: A time plot of the participants' retention in the trial.

Demographic data for all 135 randomized participants are shown in Table 1. The active treatment and placebo participants were well matched across all baseline characteristics.

Table 1: Summary of demographic and behavioral data.

Statistical Analysis

Data were analyzed using SAS/STAT 9.0 software (SAS Institute Inc, Cary, NC). Descriptive statistics were performed to compute the measures of central tendency, frequencies, percentage changes, and other distribution characteristics. An intent to treat analysis was used.

Methylamphetamine Craving

Individual craving measures are not normally distributed, therefore the nonparametric two-sample Mann-Whitney-Wilcoxon and Kruskal-Wallis tests were used to compare craving scores between the two treatment arms. For the combined craving score, the assumption of normality is not rejected, and ANOVA for repeated measures analysis of the entire trial and t-tests for individual visits were appropriate. Normality of the combined score is established by the Shapiro-Wilk test within each treatment group.

Methylamphetamine Use

Change in self-reported methylamphetamine use was determined by analyzing the change in frequency of pre- and post-treatment reports of methylamphetamine use days. The accuracy of self-reports of methylamphetamine use were assessed by analyzing the relationship between self-reported methylamphetamine use and the results of urine tests. Patterns of matches and nonmatches between self-reported use and UDS results were examined using χ^2 analysis of the 2x2 contingency table with 1 degree of freedom.

Relationship between Methylamphetamine Craving and Use

Logistic regression analysis was used to examine the relationship between methylamphetamine use and craving. Wilcoxon tests were used to analyze the number of clean urines obtained during the entire trial and the number of days of use reported by the patients. For each visit, dependence of a UDS result on the treatment received was evaluated by chi-square analysis.

Missing Data

With respect to missing post-treatment TLFB data, the most conservative approach was used. All randomized participants, regardless of whether they dropped out or completed the 30-day study, were included in the analyses which counted missing days as positive for methylamphetamine use.

Missing craving scores were treated as missing. This approach was justified by analyses which found no statistically significant differences in craving scores between the participants who dropped out of the study prematurely and those who continued to the next visit.

Adverse Events

Adverse events reported during the study were coded using COSTART and were compared between the two groups using descriptive statistics.

One-sided tests were used for each endpoint of the trial, comparing the active treatment group with the placebo group. Thus, any statistically significant differences found point to a higher efficiency of the treatment as compared with placebo (lower frequency of use, larger reduction in craving, higher percent of negative urine drug screens, etc.) On the other hand, two-sided tests were used for the analysis of

pretreatment data, verifying absence of bias, in one direction or another, in randomization of participants and treatment assignment.

Results

Methylamphetamine Craving

No differences were found at screening between the two groups with respect to baseline average craving scores (for the combined craving score, a two-sided t-test provides the t-statistic 0.92 with 133 degrees of freedom and a p-value of 0.36); for the individual visual-analogue craving measures, Kruskal-Wallis chi-square statistics range from 0.06 to 2.53, with 1 degree of freedom and p-values of 0.11 or higher).

Following the first 3 flumazenil treatments, both treatment groups experienced a statistically significant reduction in the combined craving score ($p<0.01$). At each post-infusion assessment, this score was significantly lower for participants receiving the active treatment than for the placebo group ($p<0.01$ on Day 6; $p=0.05$ on Day 13; $p=0.03$ on Day 20; $p=0.04$ on Day 30) (Table 2 and Figure 2).

The repeated measures analysis of variance over the duration of the entire clinical trial also finds significant differences between the active treatment group and the placebo group ($F=5.11$ with 1 and 74 d.f. provides a p-value of 0.02).

Table 2: Reduction in the combined craving score

Figure 2: Combined craving score of the six visual-analogue scales.

Methylamphetamine Use

Using only the most conservative analysis, with missing days counted as positive for methylamphetamine use, the active treatment participants reduced their self-reported frequency of use from 89% before the trial to 29% after the first week of the trial (Day 6) and 36% after the second week (Figure 3). Placebo participants reduced their frequency of use from 88% to 47%. The average amount of reduction among the active treatment participants significantly exceeded the average among the placebo participants (Wilcoxon rank sum statistic W=4093, p=0.02).

Figure 3: Time trends in the self-reported frequency of methylamphetamine use.

At the screening visit, the urine drug screen was positive for 98.5% of the active treatment patients and 94.0% of the placebo patients (not a significant difference; the chi-square statistic is 1.9, P=0.17). Over the 30 days of the trial, the active treatment group averaged 3.34 positive UDS results while placebo patients averaged 3.84, a statistically significant difference (Wilcoxon two-sample statistic 4119.5, P=0.02). At Day 6, again using the most conservative scenario (missing UDS counted as positive), the frequency of positive UDS decreased to 58.8% for the active treatment arm and to 79.1% for the placebo arm. The frequency of positive UDS was significantly lower for the active treatment group (Z= 2.54, P<0.01).

Figure 4: Reduction in the percent of positive (or missing) urine drug screens by Day 6.

Beyond Day 6, at every data collection visit, subjects receiving the active treatment had a lower proportion of positive UDS results, but failed to reach statistical

significance (Figure 5). On Day 13, a larger proportion of missing urine drug screens occurred in the treatment group, which when counted as positive, resulted in the observed change of pattern at this time point (Figure 5 and Table 3).

Figure 5: Time plot of positive urine drug screens.

Analysis of the overall number of clean urine samples showed that the proportion of active treatment participants with at least 1 or at least 2 negative UDS results was significantly higher than the corresponding proportion for placebo participants (Table 4). Moreover, 28 (41%) of subjects receiving the active medications and 18 (27%) placebo subjects provided two consecutive clean urines at least once, a significant difference favoring the active treatment group (Z-statistic 1.75, P=0.04). The maximum number of consecutive clean urines is also statistically significant in favor of the active treatment group (Wilcoxon statistic 4159.0, P=0.03).

Table 4: Number of clean urine samples for the two treatment arms.

Relationship between Craving Scores and Drug Use

Utilizing a logistic regression model, the combined craving score was a significant factor in predicting (a) the probability of a positive UDS on each visit and (b) the corresponding probability of abstinence between clinic visits, based on group assignment, day of the trial, and craving score. For each model (a) and (b), combined craving score was a significant predictive factor for subsequent drug use (Wald chi-square statistics 102.1 and 79.3, respectively, with 1 degree of freedom; both p-values <0.01). The average combined craving score was 11.7 for participants with negative UDS

and 35.2 for participants with positive UDS (t-statistic=19.4, p<0.01). According to self-reports, participants reporting no methylamphetamine use during the five days prior to the visit had an average craving score of 13.0, and those reporting some drug use had an average score of 34.5 (t=16.6, p<0.01).

Adverse Events

Table 5 summarizes the study-emergent adverse events reported by ≥10% of participants in either the active treatment or placebo group, using COSTART body system and preferred terms.

Table 5: Study-Emergent Adverse Events ≥10% Within Body Systems

Overall, proportions of participants reporting at least 1 adverse event were comparable, with a slightly higher percentage of occurrences in the placebo group. The active treatment group reported higher event incidence of injection site reaction, dizziness, grogginess, light-headedness, and vivid dreams than placebo. The placebo group had a higher incidence of headache. Both groups were comparable with respect to taste and olfactory perversion. Almost all the adverse events were of mild severity (treatment group = 97%, placebo = 96%); the rest were moderate with none classified as severe.

Discussion

This study evaluated the efficacy and safety of flumazenil in combination with gabapentin to reduce methylamphetamine craving in a treatment seeking population. Following the pharmacotherapy protocol using flumazenil and gabapentin, when tested in a double-blind, placebo-controlled fashion, craving was significantly reduced over the

initial 30 days of treatment. The findings confirmed similar results of a previous open-label trial (Urschel *et al*., 2007). The strong correlation between craving and drug use supports the literature regarding the importance of craving as a predictor of use and relapse (Hartz *et al*., 2001; Weiss *et al*., 2003; Rohsenow *et al*. 2007)

The improved outcome of treatment with flumazenil in combination with gabapentin may be due to restoring or altering the function of GABA-A brain receptors. There is evidence of a neurobiological basis for continued substance dependence. Pre-clinical models demonstrate an alteration in GABA-A receptors subunits during methylamphetamine exposure and withdrawal, leading to ion channel dysregulation and increased anxiety. The expression of these brain changes as the craving for and urge to use the drug is a powerful factor that may lead to relapse. In this case, the results may be generalizable to substances which are associated with GABA-A receptor dysregulation.

Though not the primary goal, methylamphetamine use data also were collected during the 30-day trial. Patients who received flumazenil plus gabapentin had lower drug use, as measured by urine drug screens and self-report, when compared with the placebo treated group. However, employing the "worst case scenario", where any missing data are counted as positive for drug use, the results failed to reach statistical significance. Engagement and retention in psychosocial treatment is critical to decreased use and long-term abstinence. Reduction of the craving and anxiety associated with substance withdrawal could allow better engagement and retention in psychosocial therapies and improved treatment outcomes, as craving and drug use have already been shown to be correlated.

The pharmacological treatment was well tolerated with almost all adverse events being of mild severity. The finding of more central nervous system COSTART categorized events is expected given that flumazenil and gabapentin are medications with central nervous system activity.

In conclusion, the present findings confirm the previously noted effect of treatment with flumazenil plus gabapentin on craving during the initial treatment of methylamphetamine dependence. Through only four weeks, a significant correlation was seen with craving being a predictor of subsequent methylamphetamine use. Considering the benefit to risk ratio, these medications may offer an option for clinicians seeking to reduce patient craving and increase engagement in psychosocial treatment. Future studies of the pharmacological protocol of longer duration and with standardized psychosocial therapy could be conducted to focus on effects on drug use.

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Legends

Figure 1: Participants' retention in the trial.

The two curves show the percent of participants remaining in the clinical trial at different time points for both treatment arms. The solid line corresponds to the percent of active treatment patients, and the dashed line corresponds to those in the placebo arm. The percent of participants retained in the study is calculated from the total number of eligible participants randomized into each arm at the beginning of the trial. Retention rates of active treatment and placebo participants are very similar: by day 30, 66% of active treatment participants and 65% of placebo participants remained in the trial.

Figure 2: Combined craving score.

The time plot shows the combined score of six visual-analogue craving measures for both treatment arms during the trial. The solid line depicts the mean craving score for the active treatment arm, and the dashed line for the placebo arm. While the difference in combined craving scores between the two groups was not significant prior to the initiation of treatment, participants treated with the active medications had significantly lower mean craving scores than placebo participants at each subsequent visit.

Figure 3: Trends in the self-reported frequency of methylamphetamine use.

The bar chart indicates the frequency of self-reported methylamphetamine use in terms of percentage of methylamphetamine use days for both treatment arms. Five pairs of bars represent the frequency of use during the 30 days prior to the initiation of treatment and during each subsequent week of the 30-day trial. In each pair, the first bar shows the frequency of use for the active treatment arm, and the second bar shows the frequency for the placebo arm. Both groups reported almost the same frequency of use prior to the trial. At every subsequent visit, participants in the active treatment group consistently reported lower frequency of use.

Figure 4: Reduction in the percent of positive (or missing) urine drug screens by Day 6.

The bar charts compare the percent of positive urine drug screens (UDS) for the two treatment arms at the screening visit and on day 6 of the trial, following the first set of infusions. The most conservative approach was used, with missing UDS results treated as positive. While the active treatment participants recorded a slightly higher percent at the screening visit, their percent of positive UDS results on day 6 day of the study is significantly less ($p<0.01$) than the corresponding percent among placebo participants.

Figure 5: Time plot of positive urine drug screens.

The two curves represent the proportion of positive UDS results estimated using the conservative approach, missing UDS results counted as positive.

Figures and Tables

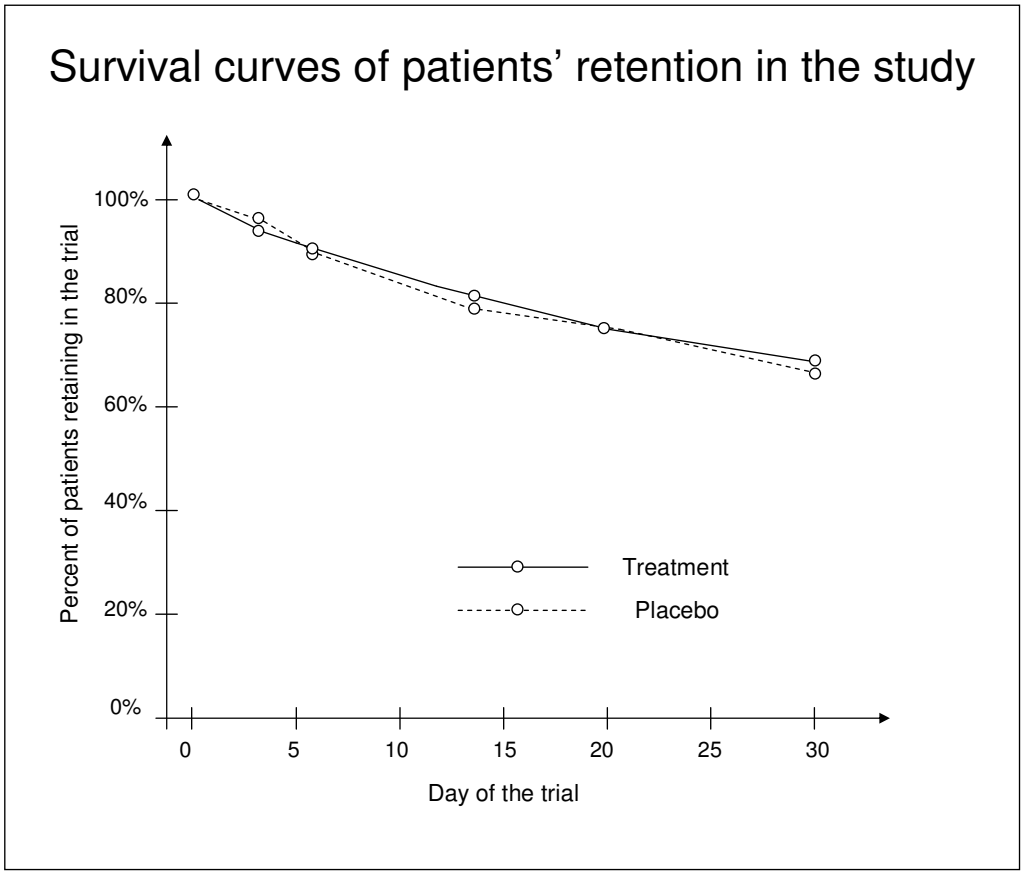

Figure 1. Participants' retention in the trial.

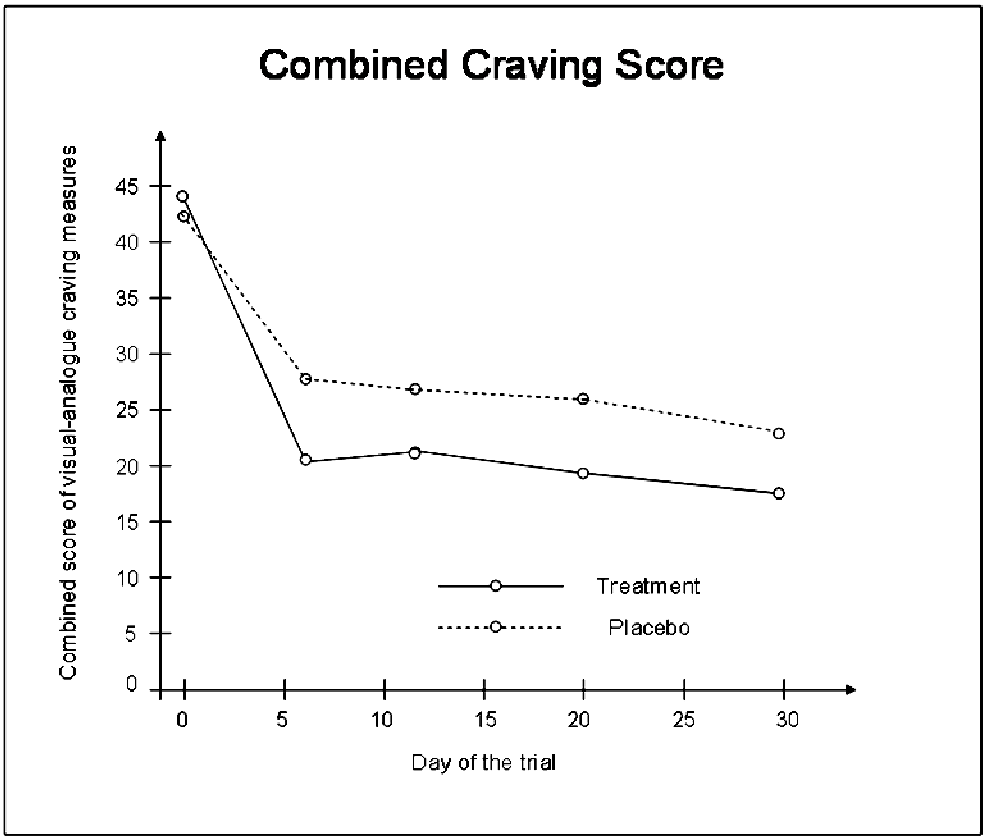

Figure 2. Combined craving score.

Table 1. Summary of demographic data.

Characteristics	Categories	Treatment group	Placebo group	P-value
Gender	Female Male	51% 49%	49% 51%	0.80
Marital status	Married Divorced, widowed Other	16% 34% 50%	24% 40% 36%	0.23
Race	Caucasian Other	93% 7%	87% 13%	0.25
Level of Education	College High school Trade school	38% 46% 16%	45% 40% 15%	0.74
Living Arrangement	Alone With spouse/partner W/ family member With roommate Other	22% 21% 25% 31% 1%	30% 31% 22% 13% 3%	0.12
Residence	Own Rent Neither	24% 38% 38%	24% 46% 30%	0.55
Employment status	Full time Part time Unemployed Other	38% 19% 32% 10%	40% 19% 34% 6%	0.84
Gross income		$20,847	$21,925	0.82
Age started drugs		21.3 years	22.1 years	0.55
Family Conflicts		4.3 days	4.0 days	0.79
Conflict others		3.2 days	2.6 days	0.52
Times Arrested		1.4 times	1.4 times	0.99

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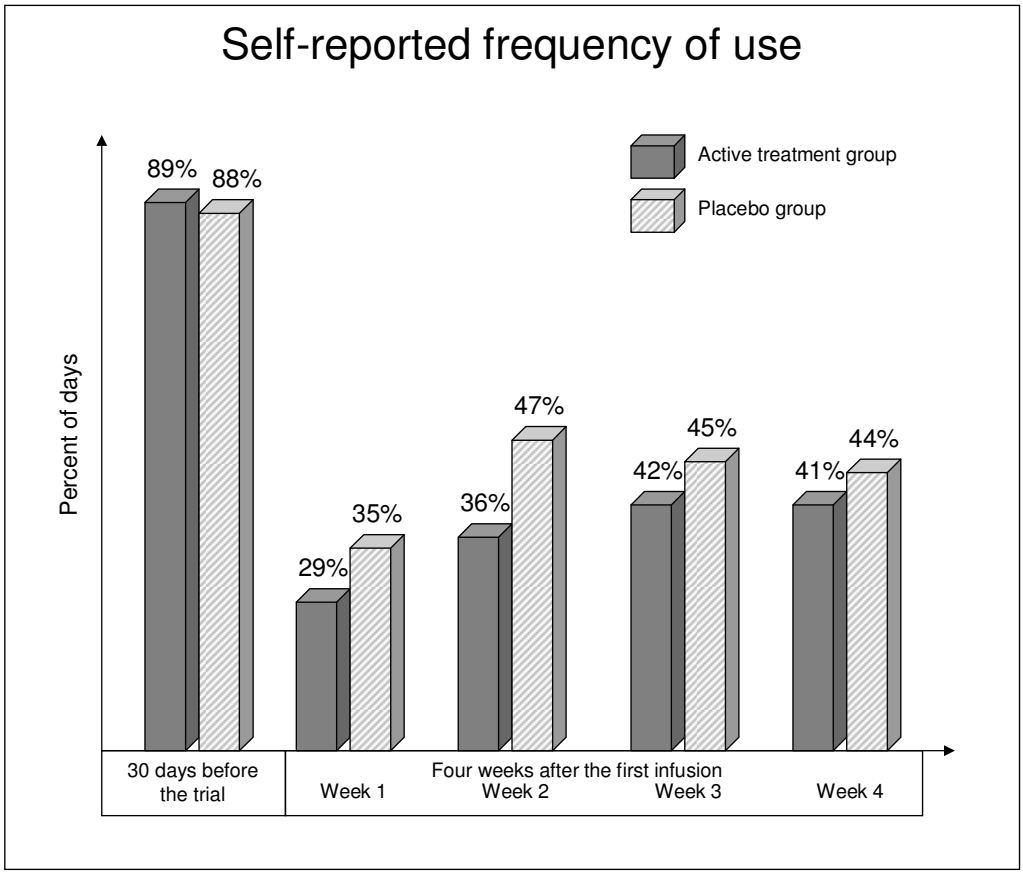


Figure 3. Time trends in the self-reported frequency of methylamphetamine use

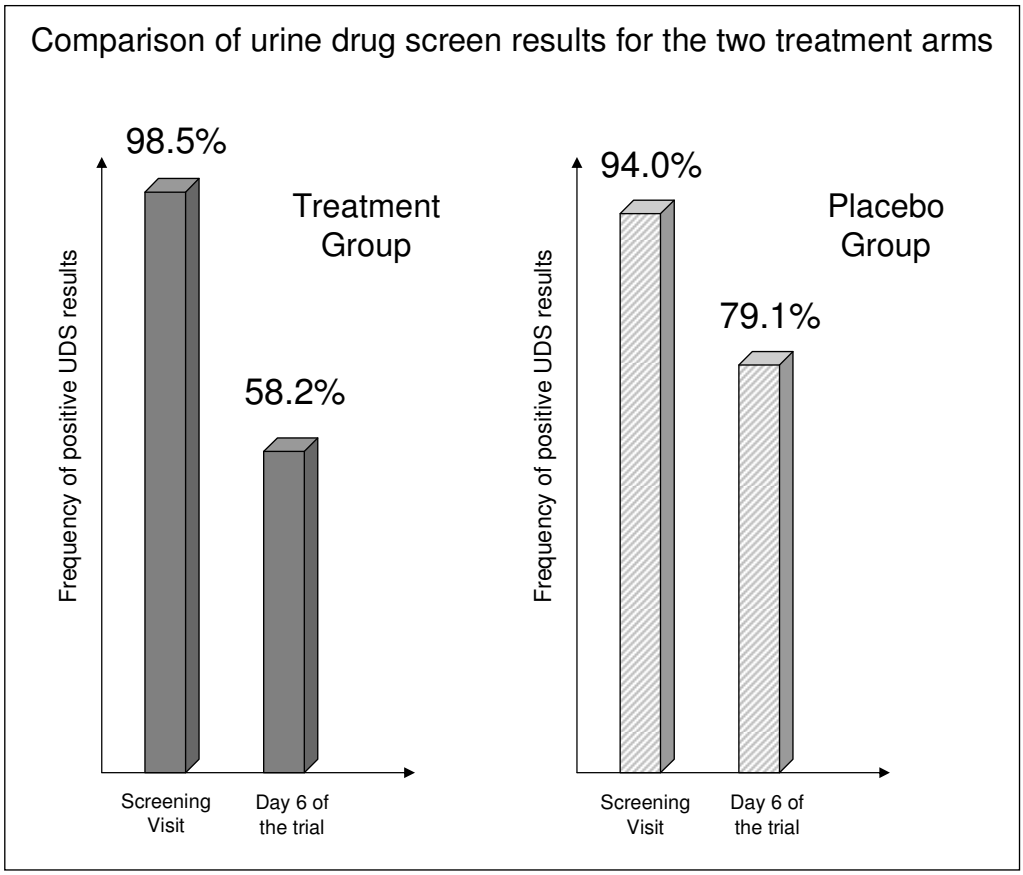


Figure 4. Reduction in the percent of positive (or missing) urine drug screens immediately following initial treatment (Day 6).

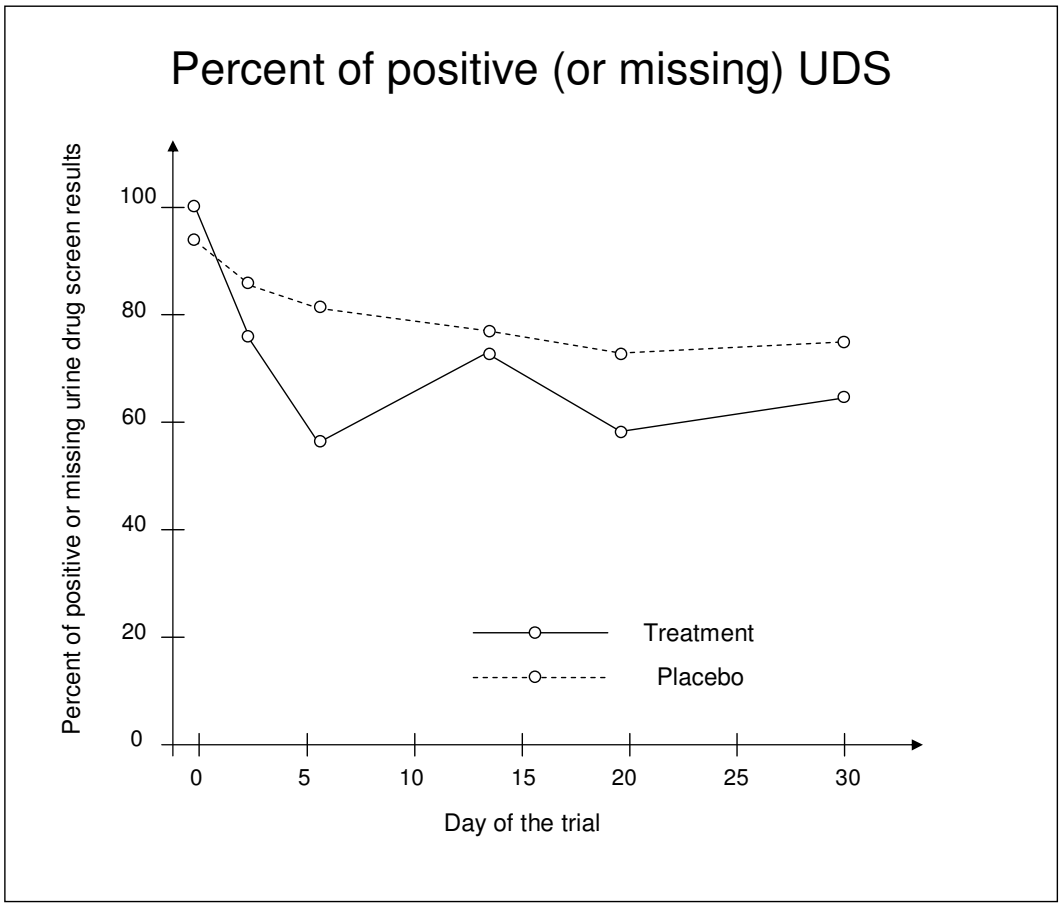


Figure 5. Proportion of positive (or missing) UDS.

Table 2: Reduction in the combined craving score (T = T-statistic, D.F. = degrees of freedom, P = P-value)

Day of the trial	Treatment Group				Placebo Group				Comparison		
	Craving	T	D.F.*	P	Craving	T	D.F.*	P	T	D.F.	P
Screening	43.7	-		-	42.5	-			0.9	133	0.36
Day 6	20.2	10.3	55	<0.01	27.6	7.2	53	<0.01	2.5	108	<0.01
Day 13	21.0	9.1	47	<0.01	26.3	8.2	47	<0.01	1.9	94	0.03
Day 20	19.0	9.2	47	<0.01	25.8	7.2	47	<0.01	2.1	94	0.02
Day 30	17.6	10.9	47	<0.01	23.6	7.8	46	<0.01	1.9	93	0.03

* Degrees of freedom are adjusted for the missing values. Only the available data are used for testing. The "missing at random" assumption is justified by the comparison of craving scores between participants competing the trial and participants dropping from it.

Table 3: Results of Urine Drug Screen tests

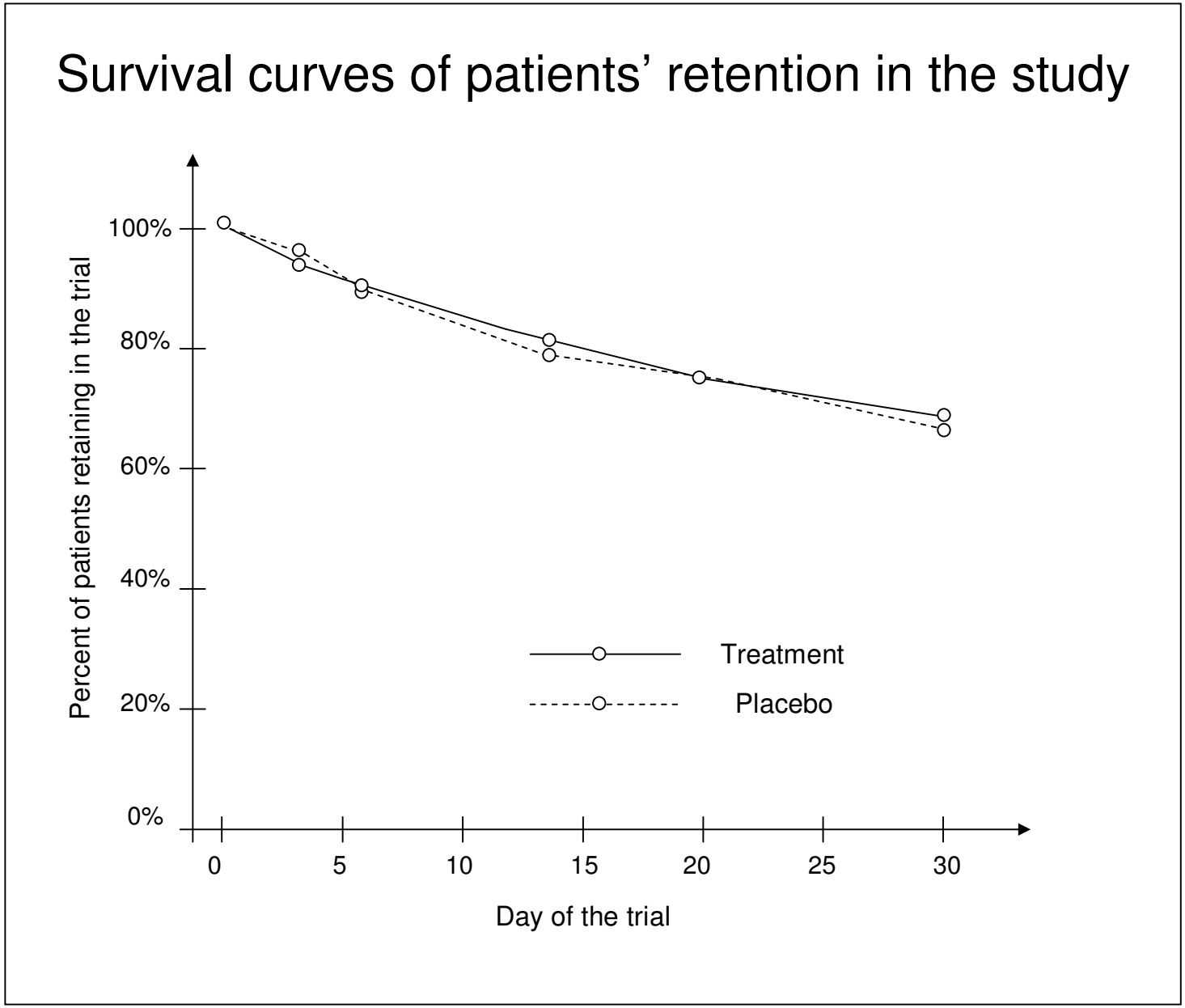
Day of the trial	Treatment Group (N=68)		Placebo Group (N=67)		P-value
	Positive UDS	Percent	Positive UDS	Percent	
Screening	67	98.5%	63	94.0%	0.17
Day 4	52	76.5%	56	83.6%	0.15
Day 6	40	58.8%	53	79.1%	<0.01
Day 13	49	72.1%	51	76.1%	0.30
Day 20	41	60.3%	48	71.6%	0.08
Day 30	45	66.2%	49	73.1%	0.19

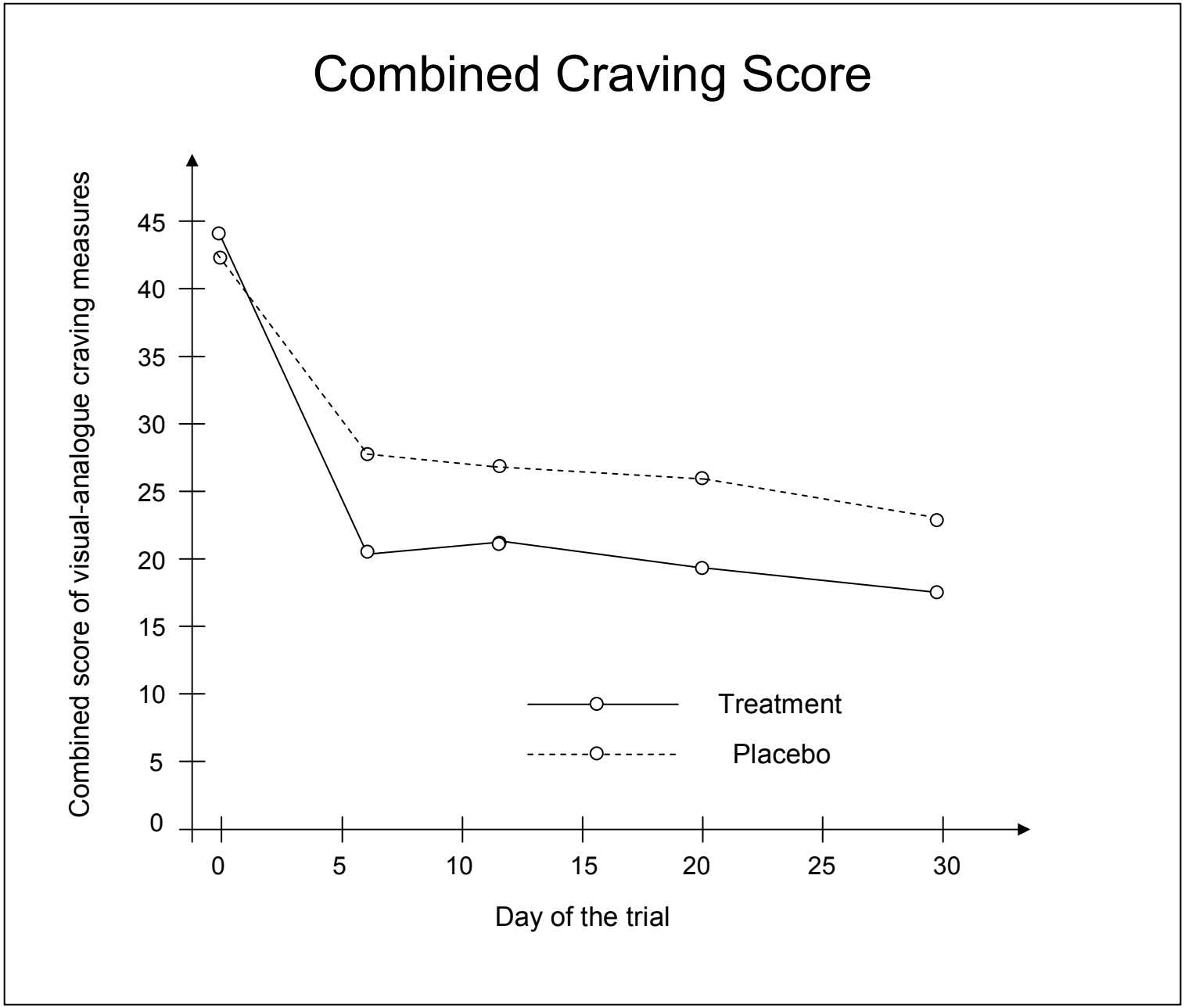
Table 4. Number of clean urine samples for the two treatment arms

Number of Clean Urines	**Treatment Group (N=68)**	**Placebo Group (N=67)**	**Z-score**	**P-Value**
At least 1	42	28	2.32	0.01
At least 2	30	19	1.90	0.03

Table 5. Study-Emergent Adverse Events ≥10% Within Body Systems

COSTART Body System	Treatment N=68		Placebo N=67	
	N	%	N	%
Participants With None	18	26.5	14	20.9
Participants With at Least One	50	73.5	53	79.1
BODY AS A WHOLE				
Fatigue	6	8.8	7	10.4
SKIN & APPENDAGES				
Coldness Local	5	7.4	16	23.9
Injection Site Reaction	32	47.1	14	20.9
NERVOUS				
Dizziness	15	22.1	2	3.0
Grogginess	7	10.3	1	1.5
Headache	8	11.8	24	35.8
Insomnia	11	16.2	8	11.9
Light-Headedness	14	20.6	4	6.0
Somnolence	9	13.2	7	10.4
Vivid Dreams	7	10.3	3	4.5
SPECIAL SENSES				
Perversion Olfactory	7	10.3	9	13.4
Taste Perversion	23	33.8	21	31.3


Survival curves of patients' retention in the study
Percent of patients retaining in the trial
100%
80%
60%
40%
20%
0%
0
5
10
15
20
25
30
Day of the trial
Treatment
Placebo


Combined Craving Score
Combined score of visual-analogue craving measures
45
40
35
30
25
20
15
10
5
0
0
5
10
15
20
25
30
Day of the trial
Treatment
Placebo

Characteristics	Categories	Treatment group	Placebo group	P-value
Gender	Female Male	51% 49%	49% 51%	0.80
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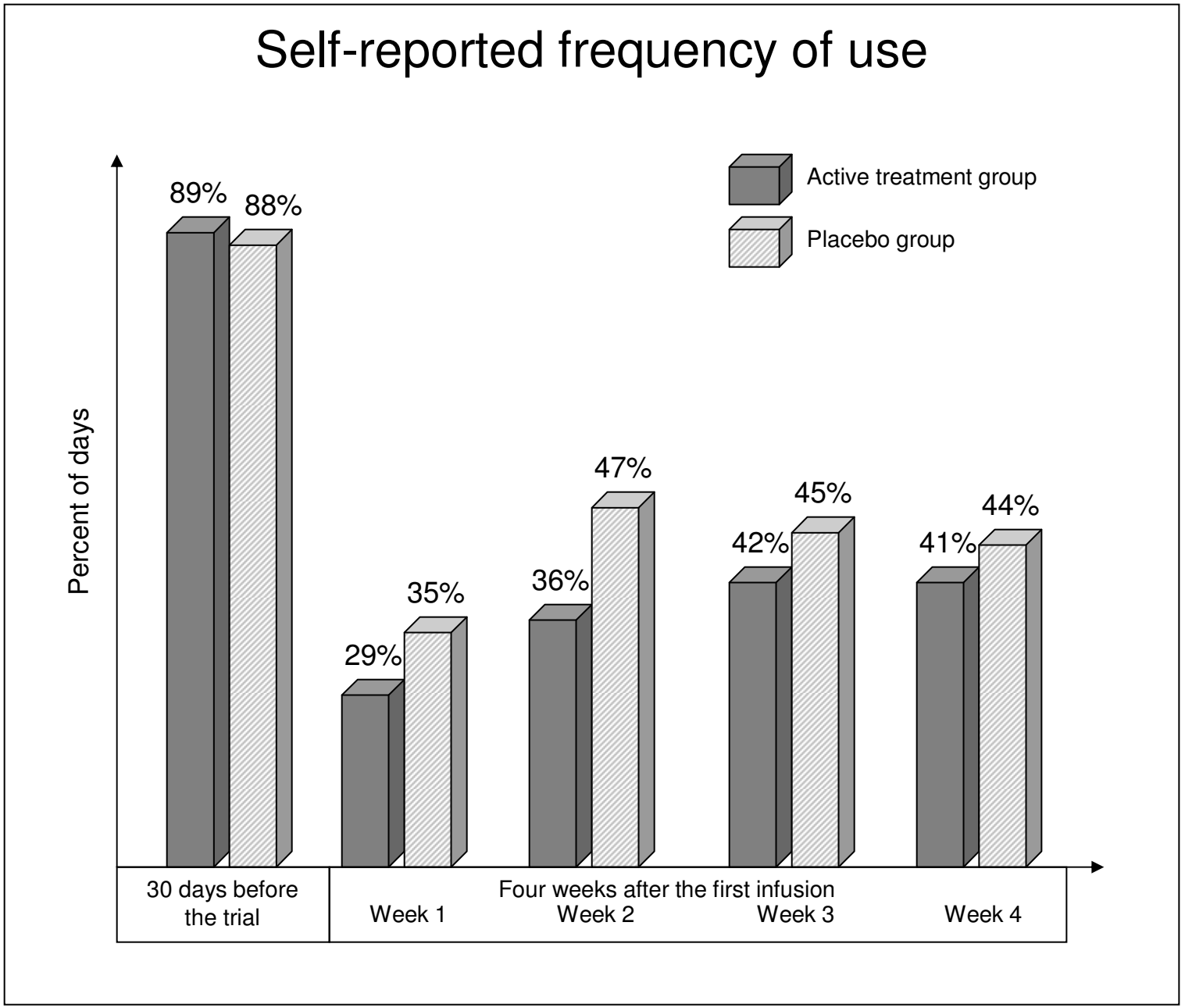
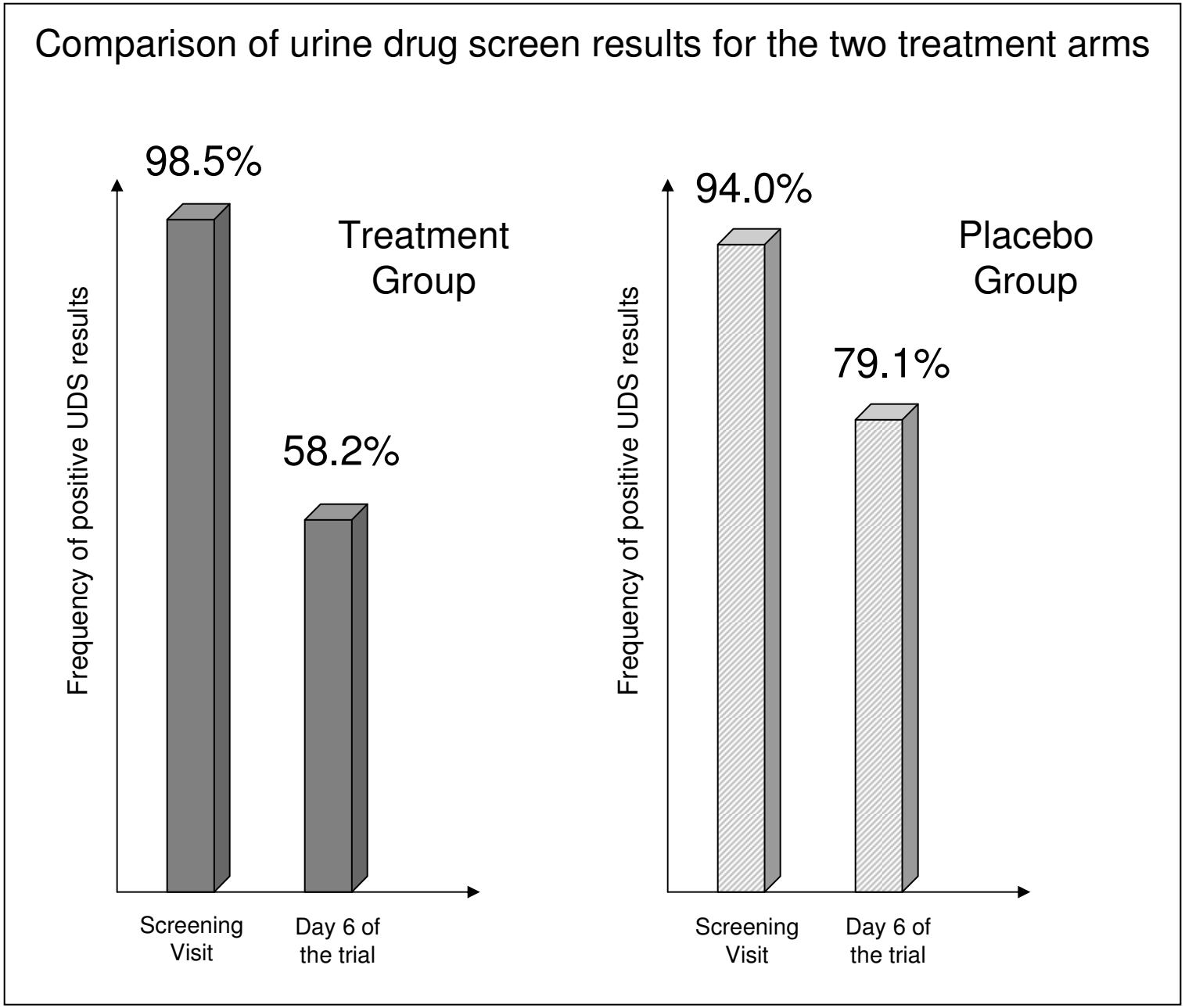
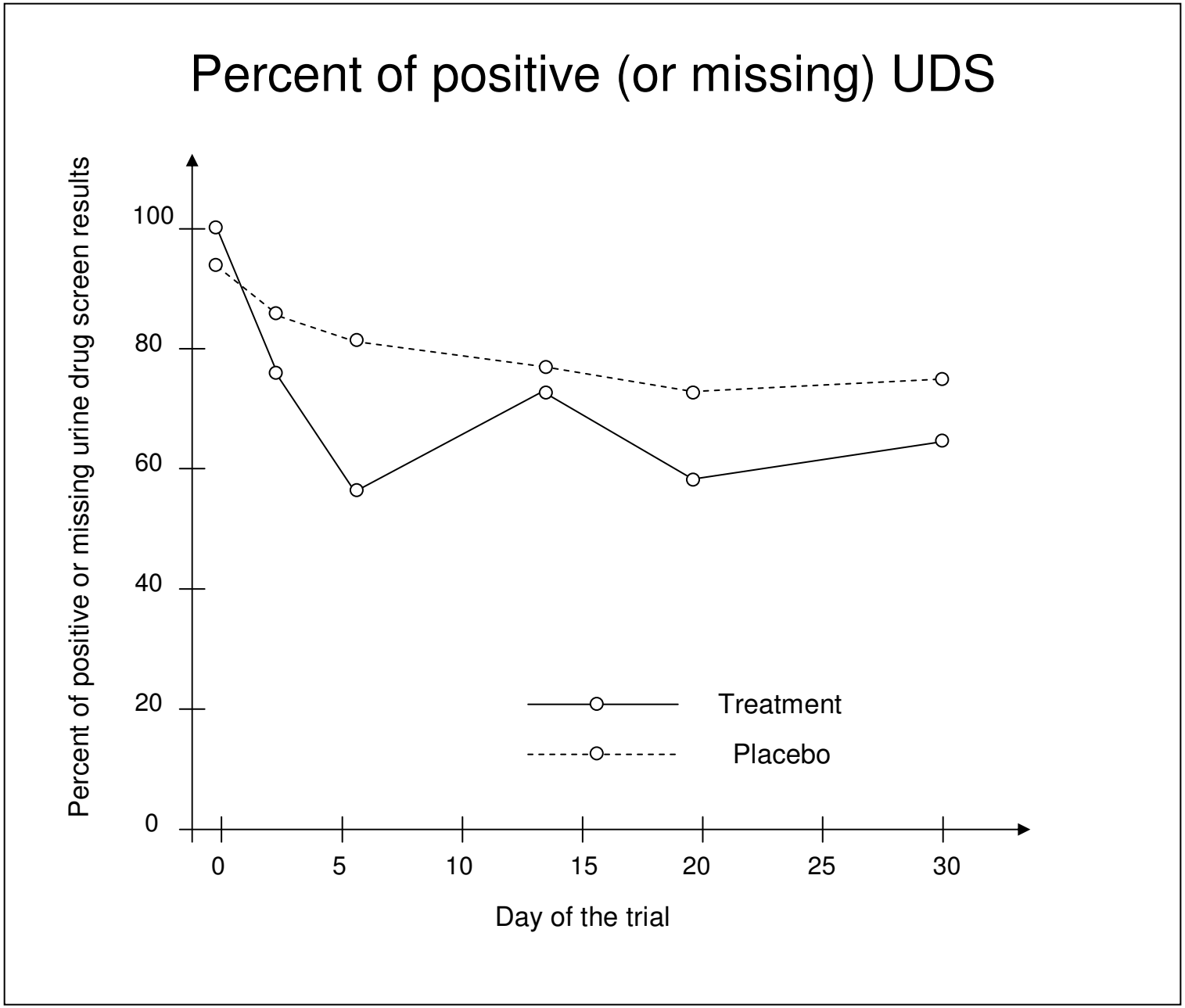

Self-reported frequency of use
Active treatment group
Placebo group
Percent of days
89%
88%
29%
35%
36%
47%
42%
45%
41%
44%
30 days before the trial
Four weeks after the first infusion
Week 1
Week 2
Week 3
Week 4


Comparison of urine drug screen results for the two treatment arms
98.5%
58.2%
Treatment Group
Frequency of positive UDS results
Screening Visit
Day 6 of the trial
94.0%
79.1%
Placebo Group
Frequency of positive UDS results
Screening Visit
Day 6 of the trial


Percent of positive (or missing) UDS
Percent of positive or missing urine drug screen results
100
80
60
40
20
0
0
5
10
15
20
25
30
Day of the trial
Treatment
Placebo

Number of Clean Urines	Treatment Group	Placebo Group	P-Value
At least 1	42	28	p<0.001
At least 2	30	19	p<0.001
At least 3	22	16	p=0.008

COSTART Body System	Treatment N=68		Placebo N=67	
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