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# Intermittent Marijuana Use Is Associated with Improved Retention in Naltrexone Treatment for Opiate-Dependence

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## Abstract

Naltrexone is a theoretically promising alternative to agonist substitution treatment for opioid dependence, but its effectiveness has been severely limited by poor adherence. This study examined, in an independent sample, a previously observed association between moderate cannabis use and improved retention in naltrexone treatment. Opioid dependent patients (N = 63), admitted for inpatient detoxification and induction onto oral naltrexone, and randomized into a six-month trial of intensive behavioral therapy (Behavioral Naltrexone Therapy) versus a control behavioral therapy (Compliance Enhancement), were classified into three levels of cannabis use during treatment based on biweekly urine toxicology: abstinent (0% cannabis positive urine samples); intermittent use (1% to 79% cannabis positive samples); and consistent use (80% or greater cannabis positive samples). Intermittent cannabis users showed superior retention in naltrexone treatment (median days retained = 133; mean = 112.8, SE = 17.5), compared to abstinent (median = 35; mean = 47.3, SE = 9.2) or consistent users (median = 35; mean = 68.3, SE = 14.1) (log rank = 12.2, df = 2, p = .002). The effect remained significant in a Cox model after adjustment for baseline level of heroin use and during treatment level of cocaine use. Intermittent cannabis use was also associated with greater adherence to naltrexone pill-taking. Treatment interacted with cannabis use level, such that intensive behavioral therapy appeared to moderate the adverse prognosis in the consistent cannabis use group. The association between moderate cannabis use and improved retention on naltrexone treatment was replicated. Experimental studies are needed to directly test the hypothesis that cannabinoid agonists exert a beneficial pharmacological effect on naltrexone maintenance and to understand the mechanism.

## INTRODUCTION

Opioid dependence is a serious public health problem, with endemic opioid dependence having been joined over the past decade by a growing epidemic of prescription opioid dependence.[1] Fortunately, effective treatments are available, but the majority of opioid dependent patients

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are not engaged in any treatment, while rates of dropout from treatment and relapse are high. Opioid substitution treatments, with methadone or buprenorphine, have consistent evidence of efficacy from multiple clinical trials, but even there rates of dropout and relapse are substantial. [2] Dropout is usually associated with relapse. Treatment failure and ongoing opioid use have serious consequences, including morbidity and mortality from overdose and infectious diseases.[3,4] Thus, factors that may improve retention deserve close scrutiny.

Factors associated with better retention in methadone maintenance include demographic characteristics of patients, such as older age, being employed, being married, having effective social supports and good health.[5,6] Importantly, features of methadone treatment programs are also associated with better outcome, including adequate methadone dosage, adequate counseling, presence of ancillary psychosocial services, emphasis on abstinence, and patient satisfaction.[7–15]

Naltrexone is a theoretically promising treatment for opioid dependence with a different mechanism of action, opioid antagonism, and potential advantages including lack of agonist effects or abuse potential. However, in practice the effectiveness of naltrexone has been severely limited by poor adherence. The ease with which naltrexone pills can be discontinued, the need for patients to be fully detoxified before starting naltrexone, and potential for precipitated withdrawal symptoms are likely contributing factors. Severity of opioid dependence and recent use of methadone have been associated with greater likelihood of dropout from naltrexone treatment.[16] Coupling of naltrexone with enhanced behavioral interventions has been shown to improve retention, but dropout rates are still high.[17–22]

We previously reported a surprising finding that opioid dependent patients with intermittent cannabis use during naltrexone treatment showed better retention than patients with either heavy cannabis use, or no cannabis use,[23] suggesting an inverted U-shaped function. This analysis was prompted by clinical observations that some opioid dependent patients on naltrexone reported benefit from cannabis use. However, this finding goes against conventional wisdom that other substance use during treatment would be associated with poor outcome, perhaps reflecting greater overall severity of addiction, or by functioning as a conditioned cue prompting return to opioid use. Other substance use is common among patients during treatment for opioid dependence,[24,25] but studies of its impact on treatment outcome have been mixed. Interestingly, a number of studies have found the impact of concurrent cannabis use on outcome of treatment for opioid dependence to be neutral.[26–28] One study found concurrent cannabis use associated with poorer psychosocial functioning, but not with dropout among naltrexone treated opioid dependent patients.[29] Another study found concurrent cannabis use associated with poorer outcome for alcohol and cocaine dependence, but not for opioid dependence.[30]

In this report, we sought to replicate the association between intermittent cannabis use and treatment retention in a different sample of opioid dependent patients undergoing naltrexone treatment, and to examine its impact on other outcomes. Since this was a randomized trial comparing intensive behavioral treatment (Behavioral Naltrexone Therapy[24,31] to a control treatment (Compliance Enhancement[32]), we also examined whether the level of behavioral treatment influences the relationship between cannabis use and outcome. We also searched for demographic and clinical differences between patients that might confound an observed relationship between cannabis use and outcome.

# METHOD

## Participants, Screening, and Procedure

The sample of patients presented in this report participated in a controlled trial of Behavioral Naltrexone Therapy (BNT) reported previously.[31] One hundred and five treatment-seeking, opiate dependent, potential participants were evaluated, of which 80 were eligible and 69 completed inpatient detoxification and were randomized. Of these, 63 patients attended at least one outpatient visit and constitute the sample under study in this report. As part of the screening procedure, potential participants were evaluated with the Structured Clinical Interview for DSM-III-R Substance Abuse Comorbidity version (SCID-SAC[33]), and by a psychiatric, medical and laboratory examination. Patients were eligible if they met DSM-IV criteria for current opiate dependence, were seeking treatment voluntarily, and had an abstinent significant other who could commit to participate in the treatment. Exclusion criteria included any unstable medical or psychiatric disorder that could make participation hazardous. After giving consent, patients were detoxified in hospital for up to 10 days, and then entered outpatient naltrexone maintenance lasting six months. Following the detoxification, patients were randomly assigned to one of two therapies: BNT or compliance enhancement (CE). All patients received oral naltrexone, titrated up to a dose of 50 mg a day, encapsulated with riboflavin to estimate compliance by urine fluorescence.

## Psychosocial Therapy

Behavioral Naltrexone Therapy, described in detail elsewhere,[24,31] is a manual-guided intervention that combines evidence-based approaches, including Motivational Interviewing, [34] Cognitive Behavioral Relapse Prevention,[35,36] Voucher Incentives,[37–42] and Network Therapy with a significant other monitoring medication-taking,[43] in an effort to optimize outcome of naltrexone treatment for opioid dependence. Its goals are to encourage continuous naltrexone adherence and abstinence from opiates. Individual treatment sessions occur three times per week for the first two weeks post-detoxification, and two times per week thereafter.

Compliance Enhancement is also a manual-guided intervention intended to control for professional attention, and to simulate standard medical management. It consists of two appointments per week, one with a psychiatrist for counseling and another for clinical monitoring. The counseling consists of psychoeducation, emphasis on compliance with daily naltrexone intake, problem-solving, and 12-step principles.[32]

## Urine Collection and Analysis

During the six months of the BNT trial urine samples were collected under supervision at each twice-weekly visit. All collected urine samples were tested for illicit opiates, cocaine, benzodiazepines, and cannabis using Abbott//MDTX and scored as positive or negative using standard NIDA cutoffs, and viewed under ultraviolet light for riboflavin fluorescence, a marker of compliance with naltrexone treatment.

## Data Analyses

Participants in the study were divided into three groups, based on how the proportion of cannabis positive urines collected during the trial was distributed. The abstinent cluster demonstrated no cannabis positive urines during their treatment (0% cannabis positive). For the intermittent use cluster between 1% and 79% of their urine samples were positive for cannabis. The consistent use cluster showed greater than 80% cannabis positive urines. Differences among the Cannabis Use groups on baseline demographics, baseline drug use, and continuous treatment outcomes were tested with chi-square or ANOVAs.

Treatment retention was the primary outcome measure. Retention was defined as the numbers of days to dropout. Patients who relapsed (reverted back to opiate dependence) or did not attend the clinic at least once within a 14-day period were rated as treatment dropouts. The day on which the patient relapsed and was removed from the trial, or the 14th day of treatment absence was designated as the time of dropout. For those completing the trial, the 182nd day was the point of censor. The effect of cannabis use on time to drop out was tested using a Cox proportional hazard model. Variables were entered into the model in three blocks. Block 1 consisted of treatment group assignment, baseline heroin use (average bags per day), and cocaine use (proportion of cocaine-positive urines during the treatment). Cocaine use (based on urine toxicology data) during the treatment differed across the three cannabis use groups thus it was entered as a control variable. Benzodiazepine and alcohol use was rare during the trial and did not significantly differ across the three cannabis use groups. In Block 2 the main effects of cannabis use were tested by the simultaneous entry of two comparisons: abstinent vs. intermittent cannabis use, and abstinent vs. consistent cannabis use. In Block 3, the moderating effect of treatment group on the relationship between cannabis use and treatment retention was tested by entering two interaction terms: a treatment by intermittent cannabis use term and treatment by consistent cannabis use term, respectively. Changes in −2 Log Likelihood statistics tested the significance of each block entry. An alpha of 0.10 was used to test the entry of the treatment by cannabis use group interaction terms in block 3.

Compliance with naltrexone treatment was calculated from the proportion of collected urine samples in the abstinent, intermittent, and consistent MJ groups that fluoresced for riboflavin under ultraviolet light. Means and standard deviations were compared by Chi-Square analysis.

To evaluate if patients changed their cannabis use during the trial, we compared baseline self-reports of the proportion of days during which cannabis was used to the proportion of cannabis positive urine toxicology collected during the trial, trichotomized into abstinent, intermittent, and consistent cannabis use categories as described above.

## RESULTS

### Sample

Among the 63 opiate-dependent patients who attended at least one post-detoxification clinic appointment, 52 (83%) were men, 11 (17%) were women, and most were Caucasian (Caucasian 54%; African-American 16%; Hispanic 30%). The average age was 35.5 years (SD = 9.2) and 81% were not in a relationship during the treatment period. The average level of heroin use was 6.5 bags per day (SD = 3.6). The majority of patients reported intranasal use of heroin. Thirty-one were randomized to CE and 32 to BNT.

No significant differences among the cannabis use groups were found concerning demographic variables, although there was a trend toward more Caucasians among the intermittent users. However, differences in baseline drug use were noted (Table 1). In the 30 days preceding entry in the trial, baseline number of heroin bags per day used increased as consumption of MJ increased across cannabis use groups. Consistent cannabis users reported a greatest proportion of cannabis use days (0.24), while intermittent users differed only slightly from abstinent users (0.06 vs. 0.01) in the proportion of cannabis use days.

### Changes in Pattern of Cannabis Use Before vs. After Treatment Entry

The pattern of cannabis use before treatment entry was classified into abstinent, intermittent, or consistent use based on self-reported use frequency at baseline and was compared to the during-treatment pattern based on urine toxicology. Sixty percent of abstinent cannabis users at baseline remained abstinent, 31% became intermittent users, and 9% became consistent users

during the trial. Thirty three percent of intermittent users at baseline remained intermittent, 11% became abstinent, and 56% became consistent cannabis users. All consistent users at baseline remained so during the trial. These data are imprecise since serial urine toxicology data were not available pre-treatment, necessitating reliance on self-report to classify pre-treatment levels. Bearing that caveat in mind, the overall pattern was for patients to either remain at the same use level, or advance to a higher level of use.

**Effect of Cannabis Use on Treatment Outcome—**Treatment outcome for the three cannabis use groups is summarized in Table 2, and the survival curves describing treatment retention across the groups are displayed in Figure 1. Intermittent cannabis users demonstrated longer treatment retention (median = 133 days) relative to those who were either abstinent (median = 35 days), or consistent (median = 35 days) users in either BNT or CE groups (log rank = 12.2, df = 2, p = .002). Cocaine use increased in proportion to the level of cannabis use, while the cannabis use groups did not differ on measures of opiate or benzodiazepine use during the treatment program. The Cox proportional hazards regression model, summarized in Table 3, yields a significant main effect of intermittent cannabis use on treatment retention, consistent with the descriptive data and the unadjusted log-rank test. Results modeling cannabis use (% THC positive urine toxicology) as a continuous variable yielded similar findings, supporting an inverted U shaped association between cannabis use and retention. There were no significant effects of baseline opioid use or during-treatment cocaine use. The model also yields a significant interaction of cannabis use level with randomized treatment condition. The interaction is driven by the heavy cannabis use group where treatment retention was better in the BNT treatment condition compared to the CE condition (see Figure 2), such that intensive behavioral therapy (BNT) appears to mitigate the adverse prognostic effect in the heavy cannabis use group, but not in the cannabis abstinent group. Compliance with naltrexone, assessed by the proportion of urine samples with riboflavin fluorescence differed by level of cannabis use ($F_{(2,60)} = 3.4$; $p < 0.03$): intermittent users (mean = 0.86, SD = 0.22), abstinent users (mean = 0.56, SD = 0.41), consistent users (mean = 0.69, SD = 0.39).

## DISCUSSION

The present study replicates a previous surprising finding[23] that intermittent cannabis use is associated with improved retention in naltrexone treatment among opioid dependent patients, while both abstinence from cannabis and regular cannabis use during naltrexone treatment are associated with high dropout. Inspection of the retention curves (Figure 1) shows that most of this effect occurs during the first 30 days after completion of inpatient detoxification and induction onto naltrexone, when dropout is steepest, and when patients may continue to experience protracted withdrawal that may be promoted by antagonist or inverse agonist effects of naltrexone.[44–46] Intermittent cannabis use was also associated with improved adherence to naltrexone pill-taking. The data comparing cannabis use levels before versus after treatment entry suggest patients either stay at the same level, or advance to a higher level of cannabis use after starting naltrexone, consistent with a process of self-medication. These findings are of interest, because they suggest the hypothesis that moderate cannabis use may be exerting a beneficial pharmacological effect improving the tolerability of naltrexone in the early weeks after induction, and that cannabinoid agonists might have promise for improving the effectiveness of naltrexone treatment for opioid dependence.

A beneficial effect of cannabinoid agonism early in the course of naltrexone treatment is biologically plausible. Rapid naltrexone induction during a 7 to 10 day hospitalization involves substantial withdrawal discomfort, which can be partially relieved by attenuating adrenergic activity with the alpha-2 autoreceptor agonist clonidine.[47,48] During the early weeks after naltrexone induction, protracted withdrawal symptoms may persist, again likely driven in part by sympathetic nervous system activation.[47,48] Data from a variety of preclinical models

suggest that exogenous cannabinoids can attenuate sympathetic nervous activation, especially with intermittent rather than sustained administration.[49–63] Thus, intermittent cannabis use might improve tolerability of naltrexone in the early weeks after induction by attenuating sympathetically driven withdrawal symptoms such as insomnia and agitation.

Cannabis also stimulates appetite and has antiemetic, antispasmodic and analgesic effects that have been clinically useful during cancer chemotherapy and wasting syndromes.[64,65] This might be useful in helping relieve the gastrointestinal distress and other physical discomfort associated with opioid withdrawal.

Finally, cannabis might improve the tolerability of naltrex-one maintenance by furnishing an indirect dopaminergic agonist effect at the brain reward system, countering the lethargy and anhedonia that are typical of opioid withdrawal and that might be worsened or prolonged by antagonist or inverse agonist effects of naltrexone. Naltrexone has not generally been associated with anhedonia among normal controls or alcohol dependent patients.[66,67] However, preclinical evidence suggests naltrexone functions as an inverse agonist in the setting of prior exposure to mu agonists,[44–46] as in opioid dependence. Cannabinoid (CB1) and mu opiate receptors are both G protein coupled receptors with overlapping neuroanatomical localization,[68] and both CB1 and mu agonists stimulate dopamine release from the meso-limbic dopamine neurons and function as positive reinforcers. Thus, cannabis might compensate for a deficit in dopaminergic tone related to naltrexone.

The hypothesis of a beneficial pharmacological effect of cannabis for naltrexone maintenance would need to account for the inverted U-shaped function, namely that heavier cannabis use was associated with worse treatment retention than intermittent use. It may be that heavy cannabis use identifies a subgroup with greater overall addiction severity and worse prognosis that overwhelms any beneficial pharmacological effect of cannabis. This would be consistent with the significant association between cannabis use level and baseline level of opioid use (bags per day) (see Table 1), which has been shown to be a predictor of poor outcome for naltrexone maintenance.[69] In prior analyses, the intensive behavioral therapy (BNT) was shown to have its greatest beneficial effect among patients with the higher levels of opioid dependence (more bags per day) at baseline.[24,70] Similarly here, the interaction of treatment assignment with level of cannabis use suggests that BNT partially counteracts the adverse prognosis in the heavy cannabis use group (Table 3, and Figure 2).

It is possible that regular or heavy cannabis use induces tolerance, perhaps through down regulation of CB1 receptors,[71] diminishing any beneficial effects. The inverted U pattern might also reflect individual differences in sensitivity to the putative beneficial effect of cannabis. Since patients would be self-medicating, in effect adjusting their own dosages, those who are most responsive to the beneficial effects might select a modest dosage level sufficient to provide substantial relief, whereas those who are less responsive may advance to more regular or heavy use without sufficient response to impact retention.

The present findings are observational, and it is also possible that the association between intermittent cannabis use and improved retention on naltrexone is accounted for by unmeasured confounds or other mechanisms, rather than a causal pharmacological effect. Baseline level of heroin use (bags per day), the most consistent predictor of naltrexone treatment in our hands,[24,69,70] was controlled for in the Cox model, suggesting severity of opioid dependence at baseline is not a confound. Another approach is to consider why patients without any concurrent cannabis use would have poor outcome. For example, it has been theorized that complete abstinence early in treatment may be stressful for patients who have long relied on substance use as a coping mechanism.[72] It is also possible that the cannabis abstinent group differs in their response to cannabis, experiencing it as either not reinforcing or aversive, based on

constitutional or neurobiological factors that also might be associated with poor response to naltrexone.

Experimental studies are needed to determine whether cannabinoid agonists may exert a beneficial effect on opioid withdrawal or naltrexone maintenance. Haney and colleagues examined the impact of naltrexone (versus placebo) on cannabis effects,[73] finding that naltrexone at 50 mg, but not 12 mg, increased the intoxicating effects of cannabis in established smokers, while in participants without a history of cannabis use, 12 mg of naltrexone enhanced the effect of cannabis.[74] Such a mechanism might explain the inverted-U pattern if naltrexone caused excessive and aversive cannabis effects among the heavy users. In any case, it suggests there may be meaningful pharmacological interactions between cannabinoid and opioid systems, and that these may be conditioned by the prior history of use.

Experimental, placebo-controlled studies are needed to directly examine whether cannabinoid agonists are effective as adjuncts to opioid detoxification or naltrexone maintenance treatment and to delineate the mechanism. Oral THC (Dronabinol) is FDA approved to counteract appetite suppression and wasting syndromes and would be available in the U.S. for study. Sativex, which includes both THC and cannabidiol, is available in Canada. Other cannabinoid agonists or partial agonists might be considered as they become available for study in the future. Small, within-subjects crossover studies in the human laboratory could examine effects of cannabinoid agonists on acute opioid withdrawal, or naloxone precipitated withdrawal. Larger placebo-controlled clinical trials should examine cannabinoid effects as adjuncts to opioid detoxification or naltrexone maintenance treatment. Success in these efforts could advance the field by improving the viability of naltrexone in the treatment armamentarium for opioid dependence. Issues regarding exposing patients to a medication with its own addictive potential would also need to be carefully addressed.

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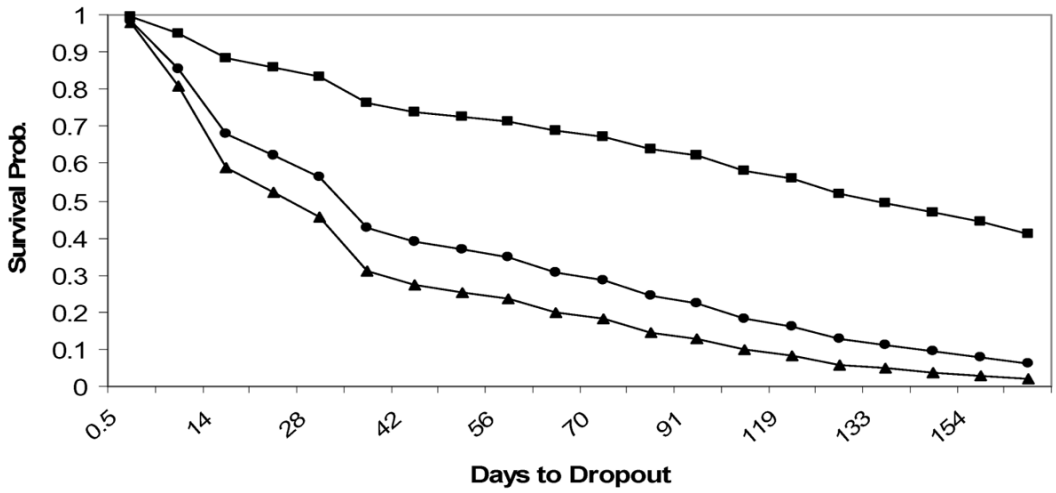


**FIGURE 1.**
Treatment retention by marijuana use pattern (Abstinent (-▲-), Consistent Use (-●-), and Intermittent Use (-■-)).

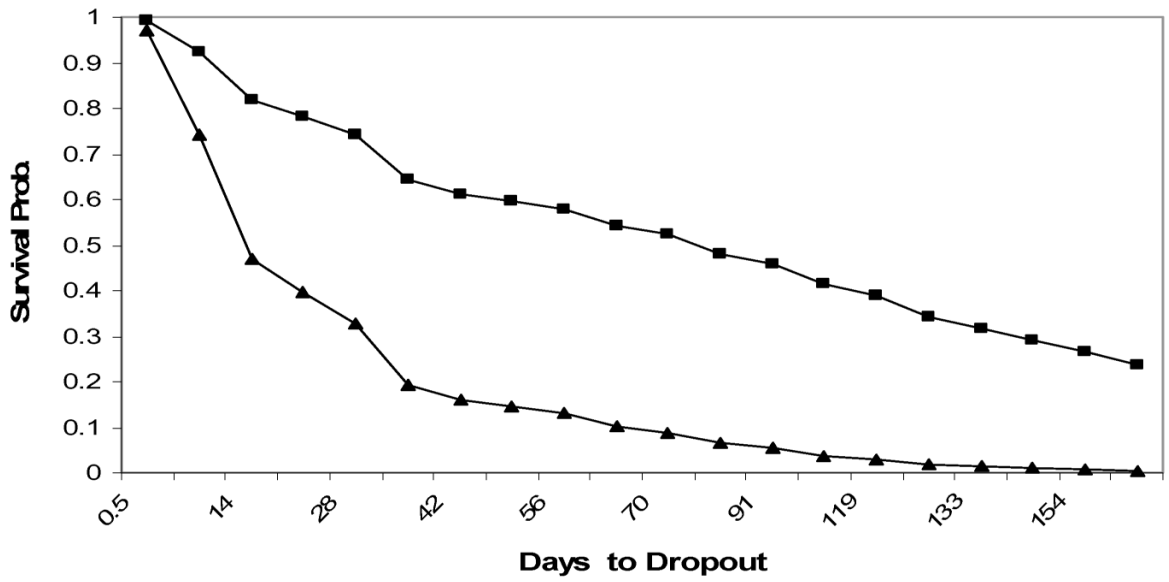


**FIGURE 2.**

Treatment retention for consistent marijuana users by treatment condition (CE (-▲-), BNT (-■-).

**TABLE 1**

Baseline demographic, drug use, treatment condition by cannabis use

| Variable | Cannabis use | | | Test statistic |
|---|---|---|---|---|
| | Abstinent (n = 24) | Intermittent (n = 18) | Consistent (n = 21) | |
| Age | 37.9 (9.23) | 35.9 (13.4) | 34.8 (9.4) | $F_{(2,60)} = 1.0$; $p < .36$ |
| Female (%) | 3 (12.5%) | 6 (33.3%) | 2 (9.5%) | |
| Relationship (%) | 7 (29.2%) | 1 (5.6%) | 4 (19.0%) | $X^2_{(2)} = 3.7$; $p < .16$ |
| Race | | | | |
| African-American | 4 (16.7%) | 1 (5.6%) | 5 (23.8%) | |
| Hispanic | 7 (29.2%) | 4 (22.2%) | 8 (38.1%) | |
| White | 13 (54.2%) | 13 (72.2%) | 8 (38.1%) | $X^2_{(2)} = 4.5$; $p < .10$[a] |
| Baseline Depression (HAM-D) | 15.0 (7.3) | 17.7 (6.8) | 15.3 (9.8) | $F_{(2,60)} = 0.4$; $p < .65$ |
| % with anxiety or depressive disorder Dx | 54% (n = 13) | 44% (n = 8) | 43% (n = 9) | $X^2_{(2)} = 0.68$; $p = .71$ |
| % with antisocial PD Dx | 88% (n = 21) | 94% (n = 17) | 86% (n = 18) | $X^2_{(2)} = 0.82$; $p = .66$ |
| Baseline Drug Use | | | | |
| Bags per day (heroin) | 5.4 (3.3) | 6.0 (1.9) | 6.7 (4.7) | $F_{(2,60)} = 3.7$; $p < .032$ |
| Proportion of days of cannabis use | 0.01 (0.03) | 0.06 (0.10) | 0.24 (0.33) | $F_{(2,51)} = 17.2$; $p < .001$ |
| Proportion of days of opiate use | 1.00 (0.00) | 0.88 (0.28) | 0.97 (0.10) | $F_{(2,51)} = 2.7$; $p < .08$ |
| Proportion of days of cocaine use | 0.02 (0.05) | 0.14 (0.28 | 0.06 (0.10) | $F_{(2,51)} = 2.5$; $p < .10$ |
| % methadone use | 92% (n = 22) | 94% (n = 17) | 95% (n = 20) | $X^2_{(2)} = .27$; $p = .88$ |
| Administration Route | | | | |
| IN | 15(62.5%) | 9 (50.0%) | 15 (71.4%) | $X^2_{(2)} = 1.1$; $p < .59$[a] |
| IV | 9 (37.5%) | 8 (44.4%) | 6 (28.6%) | |
| Smoke | 0 (0.0%) | 1 (5.6%) | 0 (0.0%) | |
| Tx Group | | | | |
| BNT | 11(45.8%) | 8 (44.4%) | 13 (61.9%) | $X^2_{(2)} = 1.6$; $p < .46$ |
| CE | 13(54.2%) | 10 (55.6%) | 8 (38.1%) | |

Note: Administration route was tested as IV versus other routes; Racial differences as Caucasian versus other.

## TABLE 2

Clinical outcome measures by cannabis use group

| Variable | Cannabis use | | | Test statistic |
|---|---|---|---|---|
| | Abstinent (n = 24) | Intermittent (n = 18) | Consistent (n = 21) | |
| Proportion of cocaine positive urines | .07 (.23) | .25 (.28) | .39 (.43) | $F_{(2,60)} = 5.2$; $p < .009$ |
| Proportion of benzodia-zepine positive urines | .07 (.21) | .06 (.15) | .10 (.21) | $F_{(2,60)} = 0.2$; $p < .85$ |
| Proportion of treatment weeks opiates were used | 0.37 (0.39) | 0.25 (0.31) | 0.39 (0.42) | $F_{(2,60)} = 0.8$; $p < .46$ |
| Median Days in treatment | 35 | 133 | 35 | Diff log rank = 12.2, df = 2, p = .002 |

**TABLE 3**

Final Cox Regression Model testing the effect of marijuana use by treatment interaction on treatment retention

| Variables | B (SE) | Wald Chi-Square | Sig | HR (95% CI) |
|---|---|---|---|---|
| Treatment | −0.390 (.36) | 1.17 | 0.761 | 0.68 (.33; 1.37) |
| Baseline opioid use (Bags per day) | 0.045 (.05) | .83 | 0.30 | 1.05 (.95; 1.15) |
| Cocaine Use during treatment | 0.030 (.50) | 0.00 | 0.95 | 1.03 (.39; 2.72) |
| Intermittent cannabis use during-treatment | −1.46 (.46) | 10.24 | 0.001 | .23 (.09; .57) |
| Consistent cannabis use during treatment | 0.351 (.54) | 0.65 | 0.516 | 1.42 (.49; 4.1) |
| Treatment × Consistent Use | −1.32 (.65) | 4.1 | 0.044 | – |