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Participant Characteristics and Buprenorphine Dose

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Abstract

Background—Clinical parameters for determining buprenorphine dose have not been adequately examined in treatment outcome research.

Objectives—The current study is a secondary analysis of data collected in a recently completed comparison of buprenorphine taper schedules conducted as part of the National Institute on Drug Abuse's (NIDA) Clinical Trials Network (CTN) to assess whether participant baseline characteristics are associated with buprenorphine dose.

Methods—After 3 weeks of flexible dosing, 516 participants were categorized by dose provided in the final dosing week (9.3% received a final week dose of 8mg buprenorphine, 27.3% received 16mg, and 63.4% received 24mg).

Results—Findings show that final week dose groups differed in baseline demographic and drug use characteristics including education, heroin use, route of drug administration, withdrawal symptoms, and craving. These groups also differed in opioid use during the four dosing weeks, with the lowest use in the 8mg group and highest use in the 24mg group ($p < 0.0001$). Additional analyses address withdrawal symptoms, and craving.

Conclusions and Scientific Significance—Final week dose groups differed in demographic and drug use characteristics, and the group receiving the largest final week dose had the highest rate of continued opioid use. These findings may contribute to the development of clinical guidelines regarding buprenorphine dose in the treatment of opioid dependence, however further investigations that include random assignment to dose by baseline characteristics are needed.

Keywords

Buprenorphine; Opioids; Treatment; Dose

Introduction

The safety and effectiveness of buprenorphine for the pharmacological treatment of opioid dependence have been established (1–8), and research continues to examine issues related to best practices for optimizing treatment outcome (9). Clinical dosing parameters for optimizing treatment outcome have yet to be empirically examined, although some buprenorphine dosing issues have been investigated, including comparable dosing, fixed vs. flexible dosing, stabilization dosages, dosing schedules, and subjective and physiological effects by buprenorphine dose.

The necessity of providing an appropriate dose is reflected in previous research comparing the effectiveness of buprenorphine and methadone which concluded that the maximum buprenorphine dose, typically 12–16mg, was too low (6, 10–14). After induction onto buprenorphine, the optimal stabilization or maintenance dose should suppress withdrawal symptoms and provide an appropriate substitute for illicit opioid use. In a meta-analysis comparing treatment outcome for methadone and buprenorphine in opioid-dependent

patients, Barnett and colleagues (15) concluded that variation between trials may be partly due to differences in dose levels, and that buprenorphine doses higher than 12mg daily may be needed to be most effective. In a non-randomized sample of methadone-maintained (n = 78) and buprenorphine-maintained (n = 76) patients, higher medication doses predicted more opioid-negative urines for both groups (16).

The advantages of flexible dosing are increasingly recognized as allowing tailored treatment to address patient needs and to ensure comfort (i.e., suppress opioid craving), and use of fixed dosing in most research designs may contribute to difficulties in interpreting study findings (12). Daily buprenorphine doses typically range from 8mg to a maximum of 24 to 32mg (5, 17), in order to provide for patient-specific needs, to minimize withdrawal symptoms, and provide an adequate maintenance dose. Buprenorphine blood concentrations typically stabilize after about 7 days of dosing (18), so emergent withdrawal symptoms may indicate that a dose increase is necessary to alleviate patient discomfort (19) and increase treatment retention.

In a unique study using flexible dosing to determine the dose required to produce an optimal therapeutic response (20), 100 opioid-dependent patients were given up to 16 weeks of buprenorphine, with daily doses ranging between 4mg and 32 mg. Using therapeutic response criteria measured by adverse events, urine toxicology, and clinic attendance, dosages were adjusted in sequential doses to reach 12, 16, 24, and 32mg per day.. Results demonstrate that, of the 50 patients who remained in treatment, 70% achieved clinical stabilization in an average of 64 days. Importantly, more than 80% of patients who achieved stabilization required more than 12mg buprenorphine per day, with a mean daily stabilization dose of 14.6mg (6.5mg). Individual variation in effective dose was apparent, although effective dose did not vary by patient characteristics.

The current study utilizes data from a NIDA Clinical Trials Network (CTN) multi-center study of buprenorphine taper schedules (9) to examine baseline characteristics and opioid use for study participants who received a daily dose of 8mg, 16mg, or 24mg during the final week of the 4-week buprenorphine stabilization/maintenance treatment phase. The final week of dosing was not assigned, but rather, participants' doses may have varied for 3 weeks until a participant-specific dose was selected by the study physician for the final week of dosing. This secondary analysis examines baseline characteristics and opioid use to determine if participants differ by final week dose. The possible identification of participant characteristics associated with buprenorphine dose has important clinical implications that could inform treatment planning and contribute to increased successful outcomes. Although this is a secondary analysis, this investigation of buprenorphine dose groups, with dose determined by clinicians after three weeks of flexible dosing, allows an examination of the association between participant characteristics, opioid use, and prescribed buprenorphine dose.

Methods

Design

Data were collected from June 2003 through November 2005 in research to compare two buprenorphine taper schedules funded by the National Institute on Drug Abuse's CTN. This was an open-label study providing four weeks of Suboxone® (combination of buprenorphine and naloxone). Following medication induction and flexible dosing for 3 weeks to determine appropriate participant-specific dose, daily dose was set at 8mg, 16mg, or 24mg buprenorphine by clinician determination for the last week of the stabilization/ maintenance phase. The current study utilizes data collected at baseline and during the 4-week stabilization/maintenance phase, before participants were randomly assigned to one of

two medication taper schedules (9). Current analyses examine whether baseline characteristics and opioid use are associated with final week maintenance dose. These analyses include data for all participants who completed the 4-week stabilization/ maintenance phase.

Participants

Eligible participants were seeking treatment for opioid dependence at one of the 11 participating treatment programs in 10 U.S. cities in Colorado, Washington, Oregon, Connecticut, New York, Virginia, and North Carolina. Two of the treatment programs were hospital-based, and 9 of the programs were Opioid Treatment Programs, although all 11 programs dispensed methadone regularly. Participants were recruited through word of mouth, advertisements, and referrals. Inclusion criteria included being at least 15 years of age, and seeking detoxification for opioid dependence. Exclusion criteria included poor general health, allergies to buprenorphine or naloxone, pregnant or nursing, having a psychiatric or medical condition that would make participation medically hazardous, dependence on alcohol or any drug other than opioids (ascertained by the DSM-IV checklist), participation in an investigational drug study in the last 30 days, or in methadone or levo-Alpha Acetyl Methadol (LAAM) maintenance or detoxification in the last 30 days. Females were required to agree to use an acceptable form of birth control. Individuals not eligible to participate were referred to local treatment facilities.

Approval was obtained from each of the participating Institutional Review Boards. All participants provided written informed consent prior to any study procedures and were compensated with $10 gift cards or cash for each weekly visit, and $25 each for screening, start of induction, start of taper, and follow-up visits.

A total of 894 participants were assessed at baseline, 83.67% (748) were inducted onto buprenorphine, and 516 completed the stabilization/maintenance phase. Analyses comparing baseline characteristics of participants who completed the 4-week stabilization/maintenance phase (n = 516) and those who dropped out before the final week (n = 232) documented significant differences in two variables. A lower mean number of days employed in the past 30 days was found for those who completed all 4 weeks (mean = 4.25, sd = 3.1) compared to those who dropped out before the final week (mean = 4.85, sd = 3.2) ($Z = 2.42$; $p = 0.0159$). A lower mean number of days of heroin use in the past 30 days was found for the retained group (mean = 22.87, sd = 11.6) as compared with the drop-out group (mean = 25.75, sd = 9.5) ($Z = 3.57$; $p=0.0004$).

Study Drug

Buprenorphine in the form of Suboxone®, a combination 4:1 ratio, buprenorphine to naloxone, sublingual tablet was used. Reckitt and Benckiser (Hull, UK) provided two formulations (2 mg buprenorphine/0.5 naloxone and 8 mg buprenorphine/2 mg naloxone) supplied by NIDA. Participants were provided weekly supplies of medications and explicit dosing instructions which included once daily dosing after induction.

Measures

Data were collected using measures and scales often included in studies of opioid treatment. The Addiction Severity Index-Lite (ASI-Lite)(22), an abbreviated version of the ASI, is a standardized clinical interview that collects problem severity profiles in seven domains commonly affected in substance abuse, including alcohol and drug use, medical, psychiatric, legal, family/social and employment/support. Demographic and drug use data collected with the ASI were used in the current analyses.

The Clinical Opiate Withdrawal Scale (COWS) (23) is an 11-item interviewer-administered measure which assesses signs and symptoms of opioid withdrawal that can be observed directly in the participant (e.g., sweating, runny nose, etc). The COWS was administered at each clinic visit, and pre- and post-dose on induction day. Scores of individual items are summed for the total score, ranging from 0–48.

The Adjective Rating Scale for Withdrawal (ARSW) (1, 24–25) is comprised of 16 self-reported signs and symptoms of opioid withdrawal rated on a scale ranging from 0 (none) to 9 (severe), with total scale scores ranging from 0–144. Item examples include muscle cramps, painful joints, and fitful sleep. The ARSW was completed at each clinic visit, with pre- and post-dose assessments on induction day.

The Visual Analog Scale (VAS) consists of 100-point lines anchored with “not at all” and “extremely.” Participants reported the extent to which they felt any craving for opioids, withdrawal symptom severity, and the extent to which the study medication helped to ease cravings. The VAS was completed at each clinic visit, and pre- and post-dose on induction day. Only the assessment of craving was used in the current analyses.

Urine samples were collected at six clinic visits: once at induction, three times during flexible dosing weeks, once during the final dose week, and once after the final dose week (before randomization to taper schedule). Samples were tested on-site with results coded as positive or negative for morphine, methadone, amphetamines, barbiturates, benzodiazepines, cocaine, methamphetamines, phencyclidine (PCP), marijuana, and tri-cyclic antidepressants. Either Jant’s Accutest MultiDrug Screen-10 or ABI’s SureStep Drug Screen Card 10A were used at each site. Additionally, use of oxycodone was assessed using ABM’s Rapid One Oxycodone single dipstick. Opioid use was measured by the Treatment Effectiveness Score (TES) (26). The TES is computed as the percentage of opioid-negative UA tests over the number of possible tests (6) during the treatment period.

Physician-prescribed daily dose was documented for each study day. Mean daily dose for each specified final week dose group are computed for these analyses.

Procedures

Induction occurred over the first three days of participation using standard induction procedures. The initial dose of study drug was determined by each study physician, but typically ranged between 2–4mg buprenorphine, with a maximum 8mg dosage for the first day. The usual dose for day 2 was 12mg, and the usual dose for day 3 was 16mg. Participants received medication to continue daily dosing until the next scheduled office visit with no more than seven days of medication provided at any time. Dose could be adjusted at weekly clinic visits, in 4mg increments, to range between 8 mg and 24 mg, as determined appropriate by the study physician.

The four week stabilization/maintenance phase included three weeks of flexible dosing to allow adjustments for individual response to buprenorphine. Although no explicit instructions were provided to physicians to determine dose, physicians may have been guided by urine test results, participants’ self-reported opioid use, as well as withdrawal, craving, and adverse events. All participants were on a daily dose of 8mg, 16mg, or 24mg by the fourth week.

Because study procedures were intended to mirror those occurring in real-life clinic settings, the behavioral treatment procedures in place at each treatment site were followed throughout the study with no attempt made to standardize or modify site-specific procedures. Efforts were made to ensure that all participants received a basic platform of substance abuse

education, and sites received self-help buprenorphine treatment booklets for distribution to participants. No data were gathered to assess engagement in the psychosocial treatment component.

Data Analysis

Baseline comparisons, dosing patterns, opioid use, treatment outcome, and withdrawal and craving are addressed. Baseline characteristics, opioid use, withdrawal symptoms and craving were compared for each dose group using chi-square and ANOVA. All associations between opioid use, withdrawal, and craving by final week dose group were analyzed using ANOVA and regression, controlling for the baseline characteristics that differed across dose groups.

All statistical tests were performed at 95% significance level. Statistical analysis was performed using SAS 9.1 (SAS Institute Inc., Cary, NC)

Results

Participants

From 748 participants meeting study eligibility and inducted onto buprenorphine, 516 completed three weeks of flexible dosing and the final week of dosing. Table 1 shows baseline demographic and drug use characteristics by final week dose. A total of 48 participants (9.3%) were prescribed final week daily doses of 8mg buprenorphine, 141 (27.3%) were prescribed 16mg, and 327 (63.4%) were prescribed 24mg. The dose groups differed in mean years of education ($F = 3.10$; $p = 0.0459$), with the 8mg dose group having more years of education (13.46 years) compared to the participants in the 16mg dose group (12.57 years) and in the 24-mg dose group (12.80 years).

The groups also differed in drug use history, including mean days of heroin use in the past 30 days ($F = 8.52$; $p = 0.0002$), with the 8mg group reporting 17.21 days (sd = 13.36), the 16mg group reporting 21.82 days (sd = 12.37), and the 24mg group reporting 24.15 days (sd = 10.70). Route of administration (injection vs. non-injection) was also significantly different (Chisq = 6.95; $p = 0.031$) with 41.67% of the 8mg group, 48.94% of the 16mg group, and 58.41% of the 24mg group reporting injection drug use. Lastly, the groups differed in baseline withdrawal and craving scores, as measured by the COWS ($F = 5.68$; $p = 0.0036$) and VAS ($F = 4.70$; $p = 0.0095$), respectively, with the 8mg group having a significantly lower score from both the 16-mg and the 24mg groups.

All study participants provided at least four urine samples of the six used to determine the TES. Of the 8mg dose group, 6.3% (3) provided 5 samples, and 93.7% (45) provided at least 6 samples. Of the16mg dose group, 1.4% (2) provided 4 samples, 12.1% (17) provided 5 samples, and 86.6% (122) provided at least 6 samples. Of the 24mg group, .31% (1) provided 4 samples, 8.6% (28) provided 5 samples, and 90.8% (297) provided at least 6 samples. Across all groups, 16 participants provided 7 urine samples, typically because of an additional clinic visit, but only one of these had all 7 samples negative for opioids. As such, the TES for this individual was rounded down to 100, whereas the TES for the other 15 participants who provided 7 urine samples remained as computed.

Dosing Patterns

Dose adjustments were allowed during the first three weeks of treatment to meet the needs of study participants in terms of discomfort, craving, and withdrawal symptoms with a final week dose of 8mg, 16mg, or 24mg determined for each participant. Mean dose prescribed for each study week by dose group is shown in Table 2.

Opioid Use

Using the TES to measure opioid use from induction through the end of the four-week treatment phase, the mean TES of the 8mg group was 66%, the 16mg group was 53%, and 24mg group was 42%. A significant association was found between final week dose group and TES after controlling for the baseline characteristics which differed by dose group (mean years of education, heroin use in the past month, COWS, and VAS) ($F=11.61$; $p<0.0001$). The 24mg dose group had greater opioid use as indicated by the smaller percentage of opioid-negative urine test results. The 8mg group had a significantly higher mean TES by 0.18 units compared to the 24mg group, and the 16mg group had a higher mean TES by 0.09 units compared to the 24mg group. The mean TES for each final week dose group is significantly different from each other.

Withdrawal and Craving

A significant association was found between final week dose group and withdrawal and craving, including the COWS ($F=19.70$; $p<0.0001$), ARSW ($F=10.16$; $p<0.0001$) and VAS ($F=22.79$; $p<0.0001$) averaged over the treatment period after controlling for the baseline characteristics that differed by final week dose group. Participants with greater withdrawal symptoms and craving scores had larger final week doses. Table 3 shows mean scores for each measure by final week dose group.

Analyses document that the 24mg group had significantly greater clinically observed withdrawal symptoms as compared to both the 8mg group ($F = 32.33$; $p < 0.0001$) and the 16mg group ($F = 31.56$; $p < 0.0001$).

ARSW scores for the 24mg group were significantly greater than for the 8mg group ($F = 15.83$; $p < 0.0001$), and for the 16mg group ($F = 25.76$; $p < 0.0001$).

VAS scores for the final week dose groups were significantly different from each other: The 8mg group reported significantly less craving then the 16mg group ($F = 7.86$; $p = 0.0052$), and the 24mg group ($F = 39.56$; $p < 0.0001$); and the 16mg group reported significantly less craving than the 24mg group ($F = 24.99$; $p < 0.0001$).

Discussion

Final week dose groups differed in baseline demographic and drug use characteristics, baseline withdrawal and craving symptoms, and opioid use during the 4-week treatment period. Because study participants' doses were based on clinical determination of participants' needs such that doses were increased or decreased through the first 3 weeks of dosing in order to identify the most appropriate dose for the final week of dosing, it might be expected that final week dose groups would experience similar rates of opioid-free urine tests results. That is, physicians were given the opportunity to provide dosage based on the apparent needs of each participant, and flexible dosing for three weeks allowed the physician to titrate up or down based on the specific participant's needs. Despite a 3-week period to identify an appropriate clinical dose, the 24mg group had the highest rate of continued opioid use compared to the 8mg and 16mg dose groups.

One explanation for these findings is that buprenorphine dose is related to severity of patients' drug use, with those having more severe drug use at baseline requiring a larger dose and, not unexpectedly, continuing to experience a higher rate of continued drug use throughout the treatment period. To compare dose groups on baseline severity of drug use, we looked at opioid use (measured by days of heroin use in the last 30 days, and route of administration) and withdrawal symptoms and craving (measured by the COWS, ARSW, and VAS) which showed significant baseline differences among dose groups. Post-hoc

regression analyses show that days of heroin use in the past 30 days significantly predicted opioid use as a function of dose. These results demonstrate that baseline severity of drug use is associated with buprenorphine dose, although no current formal assessment of drug use severity has been constructed for use at treatment intake to assist in the identification of appropriate induction and stabilization dosages. These study findings suggest that physicians may be selecting dosage based on their own expertise, with a greater dose prescribed for those with a history of more severe opiate use. Baseline assessments of withdrawal symptoms and heroin use, however, may improve the ability to assess and dispense appropriate buprenorphine dose.

A second explanation for the poorer outcome of the 24mg group is that they weren't being provided a sufficient dose given the severity of their drug use history and associated withdrawal and craving symptoms. Although the majority of study participants (63.4%) received the maximum dose of 24mg, it is unclear whether allowing for a greater dose above the study maximum of 24mg would have resulted in better outcomes for the most severely dependent participants. Published guidance on the clinical use of buprenorphine for opioid dependence (e.g., 20, 28) indicates that dosing up to 32mg daily is appropriate. Although clinical practice often resorts to an increase in dose when a patient is not doing well, a rarely used alternative option is to reduce the dose. Given the current study design, it is unknown whether study participants would have the same, better, or worse outcomes with a different final week dose.

Finally, a third possibility is that buprenorphine may not be the best pharmacotherapy for opioid dependent individuals with the most severe use history. No research has investigated the effectiveness of buprenorphine by dependence severity criteria, so it is unknown whether buprenorphine has optimal benefits only for a specific range of dependence severity. It may be that methadone maintenance is the best treatment option for patients who do not do well on even the highest doses of buprenorphine.

The mean dosage provided during the first week of treatment differs by dose groups (Table 2), suggesting that study physicians may be anticipating participants' dose needs although physicians prescribing buprenorphine may have few clinical guidelines for selecting dose. It may be that physicians opt to use a trial-by-error method, selecting a dose and adjusting up or down as deemed appropriate. Physicians may also be providing an initial low dose before increasing dose when patients do not do well.

These findings suggest that baseline assessments may aid in determining stabilization dose; particularly useful may be measures of drug use history and current withdrawal and craving indices. These findings should be investigated using other study designs that include random assignment and longer-term treatment periods. Most experts in the field would argue for longer term treatment over short-term detoxification as provided in this study, and clinicians' dosing practices may differ when providing buprenorphine for long-term maintenance treatment as compared to dosing for a short-term detoxification procedure.

Whether the results of this study examining dosages in a short-term detoxification regime would also be found in the provision of longer term treatment should be explored in future research. Other limitations that should be addressed in future research are that physicians were constrained to prescribe 1 of 3 final week dosages (8mg, 16mg, 24mg), although it is possible that an alternative dose would be most appropriate. Additionally, while the use of the TES is designed to only include opioid-negative urine results, this means that both missing and opioid-positive urine results are considered identically. This limitation is found in other research that uses urine toxicology results as a determination of treatment outcome although other reasons for missing urine tests should be considered.

The current finding that dose is related to participant baseline characteristics and continued opioid use may have important clinical implications for determining appropriate treatment plans, including daily dose of buprenorphine for the treatment of opioid dependence, but further research is required. Future research, including designs with random assignment, should be undertaken to investigate whether participant baseline characteristics can successfully predict appropriate buprenorphine dose. In addition to demographic and drug use characteristics, other participant characteristics such as co-morbidity should be included in future studies. Methods for determining optimal buprenorphine dose will be extremely helpful in clinical settings in which physicians currently have no formal tools for determining appropriate dose.

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References

1. Amass L, Kamien JB, Mikulich SK. Efficacy of daily and alternate-day dosing regimens with the combination buprenorphine-naloxone tablet. Drug Alcohol Depend. 2000; 58:143–152. [PubMed: 10669065]
2. Copenhaver MM, Bruce RD, Altice FL. Behavioral counseling content for optimizing the use of buprenorphine for treatment of opioid dependence in community-based settings: A review of the empirical evidence. Am J Drug Alcohol Abuse. 2007; 33:643–654. [PubMed: 17891657]
3. Fiellin DA, Rosenheck RA, Kosten TR. Office-based treatment for opioid dependence: Reaching new patient populations. Am J Psychiatry. 2001; 158:1200–1204. [PubMed: 11481150]
4. Fudala PF, Yu E, MacFadden W, Boardman C, Chiang CN. Effects of buprenorphine and naloxone in morphine-stabilized opioid addicts. Drug Alcohol Depend. 1998; 50:1–8. [PubMed: 9589267]
5. Ling W, Charuvastra C, Collins JF, Batki S, Brown LS Jr, Kintaudi P, Wesson DR, McNicholas L, Tusel DJ, Malkerneker U, Renner JA Jr, Santos E, Casadonte P, Fye C, Stine S, Wang RIH, Segal D. Buprenorphine maintenance treatment of opiate dependence: A multicenter randomized clinical trial. Addiction. 1998; 93:475–486. [PubMed: 9684386]
6. Ling W, Wesson DR, Charuvastra C, Klett J. A controlled trial comparing buprenorphine and methadone maintenance in opioid dependence. Arch Gen Psychiatry. 1996; 53:401–407. [PubMed: 8624183]
7. Ling W, Wesson DR. Clinical efficacy of buprenorphine: Comparisons to methadone and placebo. Drug Alcohol Depend. 2003; 70:S49–S57. [PubMed: 12738350]
8. Ling W, Amass L, Shoptaw S, Annon J, Hillhouse M, Babcock D, et al. A multi-center randomized trial of buprenorphine-naloxone versus clonidine for opioid detoxification: Findings from the National Institute on Drug Abuse Clinical Trials Network. Addiction. 2005; 100:1090–1100. [PubMed: 16042639]
9. Ling W, Hillhouse M, Domier C, Doraimani G, Hunter J, Thomas C, Jenkins J, Hasson A, Annon J, Saxon A, Selzer J, Boverman J, Bilangi R. Buprenorphine tapering schedule and illicit opioid use. Addiction. 2009; 104:256–265. [PubMed: 19149822]
10. Fischer G, Gombas W, Eder H, Jagsch R, Peternell A, Stuhlinger G, Pezawas L, Aschauer HN, Kasper S. Buprenorphine versus methadone maintenance for the treatment of opioid dependence. Addiction. 1999; 94:1337–1347. [PubMed: 10615719]
11. Kosten TR, Schottenfeld R, Ziedonis D, Falcioni J. Buprenorphine versus methadone maintenance for opioid dependence. J Nerv Men Dis. 1993; 181:358–364.

12. Mattick RP, Ali R, White JM, O'Brien S, Wolk S, Danz C. Buprenorphine versus methadone maintenance therapy: A randomized double-blind trial with 405 opioid-dependent patients. Addiction. 2003; 98:441–452. [PubMed: 12653814]
13. Petitjan S, Stohler R, Deglon JJ, Livoti S, Waldvogel D, Uehlinger C, Ladewig D. Double-blind randomized trial of buprenorphine and methadone in opiate dependence. Drug Alcohol Depend. 2001; 62:97–104. [PubMed: 11173173]
14. Schottenfeld RS, Pakes JR, Oliveto A, Ziedonis D, Kosten TR. Buprenorphine vs. methadone maintenance treatment for concurrent opioid dependence and cocaine abuse. Archives of General Psychiatry. 1997; 54:713–720. [PubMed: 9283506]
15. Barnett PG, Rodgers JH, Bloch DA. A meta-analysis comparing buprenophine to methadone for treatment of opiate dependence. Addiction. 2001; 96:683–690. [PubMed: 11331027]
16. Gerra G, Borella F, Zaimovic A, Moi G, Bussandri M, Bubici C, Bertacca S. Buprenorphine versus methadone for opioid dependence: Predictor variables for treatment outcome. Drug Alcohol Depend. 2004; 75:37–45. [PubMed: 15225887]
17. Ling W, Smith D. Buprenorphine: blending practice and research. J Subst Abuse Treat. 2002; 23:87–92. [PubMed: 12220606]
18. Chiang, CN.; Hawks, R. Development of a buprenorphine-naloxone combination drug for the treatment of drug addiction. In: Harris, LS., editor. Problems of Drug Dependence 1993, NIDA Research Monograph no. 141. Washington, DC: U.S. Government Printing Office; 1994. p. 458
19. Jones HE. Practical considerations for the clinical use of buprenorphine. Science and Practice Perspectives. 2004 August.:4–19. [PubMed: 18552728]
20. Compton PA, Wesson DR, Charuvastra VC, Ling W. Buprenorphine as a pharmacotherapy for opiate addiction. Am J Addict. 1996; 5:220–230.
21. Ling W, Hillhouse M, Domier C, Doraimani G, Hunter J, Thomas C, Jenkins J, Hasson A, Annon J, Saxon A, Selzer J, Boverman J, Bilangi R. Long suffering or prolonged suffering? Time matters. Addiction. 2009; 104:1429–1430.
22. McLellan AT, Kushner H, Metzger D, Peters R, Smith I, Grissom G, et al. The Fifth Edition of the Addiction Severity Index. J Subst Abuse Treat. 1992; 9:199–213. [PubMed: 1334156]
23. Wesson DR, Ling W. Clinical Opiate Withdrawal Scale (COWS). J Psychoactive Drugs. 2003; 35:253–259. [PubMed: 12924748]
24. Bickel WK, Stitzer MI, Bigelow GE, Liebson IA, Jasinski DR, Johnson RE. A clinical trial of buprenorphine: Comparison with methadone in the detoxification of heroin addicts. Clin Pharma Thera. 1988; 43:72–78.
25. Bickel WK, Stitzer MI, Bigelow GE, Liebson IA, Jasinski DR, Johnson RE. Buprenorphine: Dose-related blockade of opioid challenge effects in opioid dependent humans. J Pharma Exp Thera. 1988; 247:47–53.
26. Ling W, Shoptaw S, Wesson D, Rawson RA, Compton M, Klett CJ. Treatment effectiveness score as an outcome measure in clinical trials. NIDA Research Monographs. 1997; 175:208–220. PMID 9467800.
27. McCance-Katz E. Office-based buprenorphine treatment for opioid-dependent patients. Harv Rev Psychiatry. 2004; 12:321–338. [PubMed: 15764468]

Table 1

Baseline Demographic and Drug Use Characteristics by Final Week Dose Group

	Dose		
	8 mg (N=48)	**16 mg (N=141)**	**24 mg (N=327)**
Mean Age (yrs)	37.30 (10.54)	35.41 (10.03)	35.89 (10.62)
Mean Years of Education*	13.46 (2.32)	12.57 (2.29)	12.80 (2.05)
Mean number of days employed (in past 30 days)	3.56 (2.91)	4.09 (3.05)	4.43 (3.13)
Gender **Male** **Female**	64.58 (31) 35.42 (17)	64.54 (91) 35.46 (50)	68.50 (224) 31.50 (103)
Race **Caucasian** **African-American** **Others** **Hispanic**	72.92 (35) 18.75 (9) . (.) 8.33 (4)	75.89 (107) 14.89 (21) 2.84 (4) 6.38 (9)	76.76 (251) 9.17 (30) 3.36 (11) 10.70 (35)
Marital Status **Married/Remarried** **Widowed/Separated/Divorced** **Never Married**	35.42 (17) 20.83 (10) 43.75 (21)	20.57 (29) 23.40 (33) 56.03 (79)	24.16 (79) 25.08 (82) 50.76 (166)
Mean Days Heroin use (in past 30)***	17.21 (13.36)	21.82 (12.37)	24.15 (10.70)
Mean Years of Heroin use	4.54 (7.33)	6.13 (7.62)	6.82 (8.33)
Route of administration* **Non-inject** **Inject**	58.33 (28) 41.67 (20)	51.06 (72) 48.94 (69)	41.59 (136) 58.41 (191)
Mean Days Other Opioid/Analgesic Use (in past 30)	9.92 (13.33)	6.91 (11.53)	5.95 (10.66)
Mean Days Prescribed Methadone (in past 30)	0.00 (0)	0.04 (0.43)	0.03 (0.46)
Mean Days Illicit Methadone (in past 30)	0.23 (0.88)	0.47 (1.36)	0.50 (1.90)
Mean Days Cocaine Use (in past 30)	1.83 (4.89)	3.03 (6.49)	3.47 (6.93)
Mean Days Amphetamine/Methamaphetamine Use (in past 30)	0.94 94.06)	0.66 (3.26)	0.48 (2.04)
Mean Days Cannabis Use (in past 30)	4.27 (7.58)	3.98 (7.88)	4.24 (8.35)
COWS score (baseline)**	6.75 (4.01)	8.42 (3.97)	8.77 (3.89)
ARSW score (baseline)	51.83 (31.31)	61.94 (32.45)	63.78 (31.96)
VAS score (baseline)**	59.50 (24.30)	70.18 (21.77)	70.88 (25.06)

* $p < 0.05$

** $p < 0.01$

*** $p < .001$

Table 2

Mean prescribed dose for each study week by final week dose group (sd).

	WEEK			
Group	**1**	**2**	**3**	**4**
8mg n = 48	9.87 (3.6)	10.09 (4.3)	9.36 (3.5)	8.32 (1.5)
16mg n = 141	14.17 (2.9)	16.42 (2.4)	16.30 (1.7)	16.04 (1.1)
24mg n = 327	16.83 (3.3)	23.17 (2.6)	23.74 (1.3)	23.92 (0.4)

Table 3

Mean (and standard deviation) scores for withdrawal (COWS, ARSW) and craving (VAS) for entire treatment phase and for each treatment week by final week dose group.

Dose	Wks. 1–4	Wk. 1	Wk. 2	Wk. 3	Wk. 4
COWS					
8-mg	1.34 (1.04)	2.11 (1.73)	1.04 (1.11)	0.98 (1.47)	0.96 (1.50)
16-mg	1.75 (1.12)	3.18 (2.03)	1.38 (2.08)	1.07 (1.49)	0.86 (1.18)
24-mg	2.47 (1.38)	4.69 (2.75)	1.87 (1.90)	1.50 (2.04)	1.22 (1.68)
ARSW					
8-mg	14.51 (12.24)	22.03 (17.77)	13.87 (16.84)	12 (15.89)	9.57 (12.33)
16-mg	16.21 (14.15)	29.17 (22.96)	12.71 (16.71)	10.74 (14.89)	8.93 (13.96)
24-mg	24.59 (17.76)	41.62 (26.79)	21.04 (22.06)	17.50 (21.54)	14.41 (18.69)
VAS					
8-mg	10.62 (9.69)	17.3 (15.76)	6.43 (9.37)	4.57 (6.13)	11.87 (24.99)
16-mg	18.67 (17.19)	31.86 (22.87)	15.73 (21.96)	12.77 (20.92)	9.97 (16.93)
24-mg	27.33 (18.00)	45.32 (24.73)	23.76 (23.63)	19.54 (25.11)	16.4 (22.67)