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Buprenorphine tapering schedule and illicit opioid use

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Abstract

Aims—To compare the effects of a short or long taper schedule after buprenorphine stabilization on participant outcomes as measured by opioid-free urine tests at the end of each taper period.

Design—This multi-site study sponsored by Clinical Trials Network (CTN, a branch of the US National Institute on Drug Abuse) was conducted from 2003 to 2005 to compare two taper conditions (7 days and 28 days). Data were collected at weekly clinic visits to the end of the taper periods, and at 1-month and 3-month post-taper follow-up visits.

Setting—Eleven out-patient treatment programs in 10 US cities.

Intervention—Non-blinded dosing with Suboxone® during the 1-month stabilization phase included 3 weeks of flexible dosing as determined appropriate by the study physicians. A fixed dose was required for the final week before beginning the taper phase.

Measurements—The percentage of participants in each taper group providing urine samples free of illicit opioids at the end of the taper and at follow-up.

Findings—At the end of the taper, 44% of the 7-day taper group (n = 255) provided opioid-free urine specimens compared to 30% of the 28-day taper group (n = 261; P = 0.0007). There were no differences at the 1-month and 3-month follow-ups (7-day = 18% and 12%; 28-day = 18% and 13%, 1 month and 3 months, respectively).

Conclusion—For individuals terminating buprenorphine pharmacotherapy for opioid dependence, there appears to be no advantage in prolonging the duration of taper.

Keywords

Buprenorphine; buprenorphine taper; opioids; opioid dependence; treatment

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Declarations of interest
None.

INTRODUCTION

Clinical research in the last 10 years has established buprenorphine as a safe and effective alternative to methadone [1–7], producing significant and substantial improvement over time in psychosocial functioning [8]. As a high-affinity, partial μ-opioid agonist, buprenorphine was approved by the US Food and Drug Administration in 2002 as a pharmacotherapy for opioid dependence [9]. Typically, treatment with buprenorphine in the United States utilizes Suboxone®, a sublingual combination tablet containing buprenorphine and naloxone in a 4: 1 ratio [10–13], a formulation developed to help inhibit diversion and intravenous abuse of buprenorphine.

Buprenorphine has unique features that make its use possible in physician office settings [14], which may alter current strategies for maintenance and detoxification for opioid-dependent individuals [7,15,16]. In particular, buprenorphine's ceiling effect decreases the danger of overdose [17], may limit its abuse liability [17,18] and confers low toxicity, even at high doses [19,20]. Buprenorphine can also produce sufficient tolerance to block the effects of exogenously administered opioids [18,21], thus reducing illicit opioid use. Finally, buprenorphine's slow dissociation from μ-opioid receptors results not only in a long duration of action, but also diminishes symptoms and signs of withdrawal upon cessation [22,23], permitting accelerated tapering schedules.

As of mid-2008, 8777 physicians in the United States were prescribing buprenorphine to treat opioid dependence [24], and it is likely that pharmacotherapy with buprenorphine will increase as more clinicians become aware of office-based treatment using the Suboxone® formulation. As the use of buprenorphine increases it is imperative to understand the most effective methods of use, including the most appropriate methods for tapering an individual off buprenorphine.

Most clinicians in the United States who use buprenorphine as a treatment tool for opioid-dependent patients plan for eventual medication withdrawal, and tapering a patient off a stable buprenorphine dose is a common event in clinical practice. Little empirical research has addressed the effect of the buprenorphine tapering schedule on clinical outcomes, particularly the maintenance of abstinence, to guide the selection of a buprenorphine tapering schedule. Findings from a recent study by Becker *et al.* [25] indicate that a 28-day taper schedule is associated with promising outcomes in a small sample. In contrast, variable taper periods [26] and ultra-short taper periods [27] have been utilized. Amass *et al.* [22] examined specifically whether buprenorphine taper duration influenced treatment outcomes. Opiate-dependent individuals (n = 8) were stabilized on buprenorphine for 28 days before being randomized to either a 36-day taper or a 12-day taper. In this small sample the longer taper schedule was more advantageous, as indicated by withdrawal symptoms and opiate-free urines across the taper period.

The study described here compared two taper schedules following a period of physiological stabilization on buprenorphine (Suboxone®) in a large, representative sample of opioid-dependent individuals. The multi-site study was set in 11 sites in 10 US cities, and was conducted as part of the Clinical Trials Network (CTN), a subgroup of the US National Institute on Drug Abuse. The study sought data that could clarify the primary issue of concern regarding buprenorphine cessation, specifically the effect of taper duration on opioid use.

Following the findings of Amass *et al.* [22], we hypothesized that a longer taper schedule would result in a higher percentage of participants providing opioid-free urine samples at the end of the taper. We chose taper schedules of 7 and 28 days to approximate the same relative length of time between conditions as Amass [22], while providing practical

considerations for clinicians and patients by shortening the periods slightly and conforming to a precise number of weeks for each condition.

METHODS

Sample characteristics

A total of 990 individuals agreed to participate in the study, and 894 individuals were eligible to participate based on initial screening. A total of 748 participants were inducted onto Suboxone®, although 232 participants terminated or were dropped at some point during the induction/stabilization phase due to missed visits, a desire to stay on Suboxone®, etc. Thus, 516 participants were randomized to the 7-day (n = 255) or 28-day (n = 261) taper. All analyses included data from participants who were randomized at the end of the maintenance/stabilization period (n = 516). No statistically significant demographic or drug use differences were found between the two taper groups at baseline (all comparisons $P > 0.05$). The mean age of participants was 35.8 and 36.0 for the 7-day and 28-day groups, and the percentage of females in both taper groups was identical at 32.9%. Ethnicity also did not differ between the groups, with 78.8% and 73.6% whites, 12.6% and 10.7% African Americans and 4.3% and 8.1% Hispanics in the 7-day and 28-day groups, respectively. The mean number of years of education in both groups was 12.8 years, and the percentage of participants unemployed in the last month was 31.0% and 39.1% for the 7-day and 28-day groups, respectively. Total life-time drug use and drug use in the 30 days before screening were not statistically different between groups. For example, both groups reported a mean of approximately 28 days of heroin use in the last 30 days [standard deviation (SD) = 5.45, 5.34] and about 8 years of life-time heroin use (SD = 8.99, 7.53). The taper groups also did not differ in self-reported or clinically assessed withdrawal symptoms, or self-reported craving at baseline or randomization ($P > 0.05$ for all comparisons). The two groups did not differ in opioid use (measured using the percentage of opioid-negative urine test results over the possible urine test results) during the stabilization period (t = 1.02; P = 0.3087). Further comparisons document that the two taper groups did not differ in the number of concomitant medications used for withdrawal symptoms reported as adverse events during the stabilization period ($P > 0.05$). χ^2 and t-tests were used to compare the group of participants who remained in the study until the end of the taper with those who dropped out before the end of the taper. The two groups were not statistically different in demographic and drug use characteristics.

Design

This was a randomized, parallel-group, open-label study in which all procedures were identical for all participants until the taper period. After completing the consent process and baseline assessments, participants were inducted onto buprenorphine (Suboxone®) according to clinical practice, and stabilized on dose during the 4-week stabilization period. After the induction/stabilization phase, participants were assigned randomly to either a 7-day or 28-day tapering regimen (Table 1).

Participants completed weekly data collection to week 8, including the 4 induction/stabilization weeks and 4 successive weeks, so that participants in both conditions had the same number of data collection visits. Participants in both groups also attended clinic once weekly for 4 weeks after starting the taper (post-randomization) to maintain equivalence in the number of clinic visits across the two taper groups. For the 7-day taper group, medication provision ended at day 7, and medication provision extended to day 28 for the longer taper group. Follow-up interviews occurred at 1 month and 3 months post-taper.

The maximum length of study participation was approximately 5 months, including screening, induction/stabilization, taper and follow-up phases. Participants were encouraged to participate in the psychosocial treatment program administered at the treatment site (treatment as usual; TAU). Because this trial was designed to reflect real-world practice, no effort was made to standardize the psychosocial services or require participation in the psychosocial component. Following the taper, participants could continue in TAU or be referred to other local treatment resources.

The primary outcome was the percentage of participants in each taper group who were present and provided urine samples free of illicit opioids at the end of the taper period, and again at 1-month and 3-month follow-up assessments. Secondary outcomes included group comparisons of use of all drugs; withdrawal scores; the number of concomitant medications used to treat withdrawal symptoms; craving scores; and treatment satisfaction scores.

Participants

Recruitment began in June 2003 and data collection was completed in November 2005. Eligible participants were at least 15 years of age, and seeking treatment for opioid dependence at one of the 11 participating treatment programs in 10 US cities in Colorado, Washington, Oregon, Connecticut, New York, Virginia and North Carolina. Methods of recruitment included word of mouth, radio announcements, newspaper advertisements and referrals from local opioid treatment and outreach programs, alcohol and drug abuse clinics, primary care providers, local mental health centers, crisis clinics and hospital emergency rooms.

Participants were excluded if they provided a urine sample testing positive for methadone or benzodiazepine, were in poor general health, had a self-reported allergy to buprenorphine or naloxone, were pregnant or nursing, or had a medical or psychiatric condition that could make participation unsafe. Participants were also excluded if they were dependent on alcohol or any drug other than opioids (per DSM-IV criteria), or had participated in an investigational drug study, or methadone or levo-alpha acetyl methadol (LAAM) maintenance or detoxification in the previous 30 days. Pending legal action and inability to remain in the area also precluded participation. Females of childbearing potential could participate if they agreed to use an acceptable form of birth control.

All ineligible individuals were referred to standard treatment services within the community treatment program (CTP) or another local treatment facility, as determined appropriate by the CTP staff. The study was approved by each of the participating Institutional Review Boards and the Human Subjects Protection Committee at the University of California, Los Angeles (UCLA), as UCLA investigators were the lead group overseeing the study. All participants provided written informed consent prior to any study procedures. Cash and grocery tokens were used as participant incentives based on site preferences or site Institutional Review Board requirements. Participants received $25 for each ‘milestone’ visit (screening, start of induction, start of taper, follow-up visits), $10 for each weekly clinic visit and $25 for completion of all post-taper visits. Generally, the maximum incentive available was $185, although one site provided up to $210.

A priori sample size calculation indicated that 240 participants in each group would provide 82% power to detect a 12% difference, assuming 20% opioid-free urine samples in one group [12]. With 20% dropout, 72% power to detect a 12% difference would be retained.

Measures

After providing informed consent, participants completed multiple questionnaires, as well as physical examinations and medical and laboratory testing, to determine study eligibility and

to provide baseline information. Eligible individuals were scheduled for induction onto the study medication. Study measures included the following:

1. *The Adjective Rating Scale for Withdrawal* (ARSW) collected self-report information on 16 signs and symptoms of opioid withdrawal [1,7,21] (e.g. muscle cramps, nausea, etc.) rated from 0 (none) to 9 (severe) for each item, with a maximum possible score of 144 indicating the most severe withdrawal experience. The ARSW required 5 minutes to complete and was administered at each data visit.

2. *The Clinical Opiate Withdrawal Scale* (COWS) is an 11-item questionnaire [28] providing a description of signs and symptoms of opiate withdrawal that are observed clinically (e.g. sweating, runny nose, etc.). A clinician completed the COWS at each data visit with a possible total score ranging from 0 (none) to 48 (severe).

3. *The Visual Analog Scale* (VAS) is a self-report measure that assesses the extent to which the participant feels any craving for opiates, the severity of withdrawal symptoms, and the extent to which the study medication helps to ease cravings (if applicable). Three 100-point lines anchored with ‘not at all’ at one end and ‘extremely’ at the other [29,30] are included. The VAS takes about 1 minute to complete and was administered at each data visit.

4. *The Addiction Severity Index-Lite (ASI-Lite)* is a standardized, multi-dimensional clinical interview to collect information on problem severity profiles in domains affected commonly by substance abuse [31]. The Lite version is an abbreviated format with assessment domains including general demographic information, alcohol use, drug use, medical, psychiatric, legal, family/social and employment/ support. To collect additional information not included on the ASI, such as nicotine use and a distinction of illicit and prescribed methadone use, a one-page addendum was constructed and administered as a companion to the ASI. The ASI-Lite and the additional assessment were administered at baseline and at the 1-month and 3-month follow-up visits.

5. *The Satisfaction Questionnaire* (SQ) collected self-report information about the clinic, medication and treatment and recovery. The current nine-item version is an abbreviated version of the CSQ [32], using a 10-point scale ranging from 1 = not satisfied to 10 = very satisfied. The SQ was administered at the end of taper and at the 1-month and 3-month follow-up visits.

6. *Concomitant medications* include number and types of non-study medications used by participants, including prescription and over-the-counter medications and herbal remedies. Only data documenting concomitant medications used for withdrawal symptoms were used in these analyses.

7. *Urine drug screens* tested urine samples collected weekly at each clinic visit and tested on-site, adhering to standard testing protocol. Methods to ensure accurate results included using temperature strips and reading results during an appropriate time window. Results were coded qualitatively as positive or negative for morphine, methadone, oxycontin, amphetamines, barbiturates, benzodiazepines, cocaine, methamphetamine, phencyclidine (PCP), marijuana and tricyclic antidepressants. Jant’s Accutest MultiDrug Screen-10 or ABI’s SureStep Drug Screen Card 10A was used at each site. All sites also tested for oxycodone with ABM’s Rapid One Oxycodone single dipstick.

Procedures

Study medication—Suboxone® is a combination buprenorphine and nalox-one sublingual tablet at a ratio of 4: 1. Reckitt & Benckiser (Hull, UK) provided two formulations (2 mg/0.5 mg and 8 mg/2 mg buprenorphine/naloxone), supplied to the sites by the National Institute on Drug Abuse. Participants were given weekly supplies of Suboxone® and explicit dosing instructions.

Psychosocial TAU—Study procedures were intended to mirror those occurring in 'real-world' clinic settings. As such, the psychosocial treatment procedures in place at each site were provided throughout the study with no attempt to standardize or modify site-specific TAU procedures. The study protocol required that participants receive a basic platform of substance abuse education, and all sites provided self-help buprenorphine treatment booklets. No data assessed engagement in the psychosocial treatment component.

Medication induction—To facilitate transition onto Suboxone®, each participant was instructed not to use any heroin or other opioids for at least 6 hours prior to the time scheduled to receive their first dose of Suboxone®. Induction occurred over the first 3 days of the study. The study physician dispensed the first dose of 2 mg or 4 mg (expressed as amount of buprenorphine) to the participant, who was instructed to hold the tablet sublingually until the medication had dissolved. The initial dose was determined by each study physician based on his/her experience with this drug and the needs of the participant, although no documentation was made of the rationale for each dosing determination. Participants remained in the clinic for at least 1 hour after dosing for monitoring of adverse effects. An additional dose could be provided in the clinic at the study physician's discretion, with a maximum dosage of 8 mg for the first day. The physician dispensed enough medication to each participant to continue dosing until the next scheduled office visit, with no more than 7 days' dosage provided at any time. Research staff contacted the participant by telephone on day 2 to address adverse effects, withdrawal symptoms and craving. This contact was intended to confirm the participant's wellbeing in the first days of study drug use, and no script was used. The maximum dosage for the second day of induction was 12 mg, and 16 mg was the maximum dosage for day 3. Participants attended the clinic and saw study medical staff at least one additional day during the first week for evaluation of vital signs, drug use, craving, withdrawal symptoms, over-medication, adverse events and concomitant medication use. At these visits, medication dosage could be adjusted by the study physician, in 4 mg increments, to range between 8 mg and 24 mg. The study physician prescribed concomitant medications at his/her discretion if a participant complained of withdrawal symptoms.

Stabilization—The 4-week induction/stabilization period included 3 weeks of flexible dosing. Prievious clinical trials suggest that individuals vary in tolerance and response to Suboxone® doses [33]. Flexible dosing permitted physicians and participants to determine the most effective dose while considering subjective effects such as withdrawal symptoms, craving and physical status. At each scheduled weekly visit during this period, the study physician could adjust the participant's dose in increments of 4 mg. The maximum allowable dose was 24 mg per day, and the minimum was 8 mg per day. A change in dose could be made after assessing the participant's vital signs, evaluating illicit drug use (by self-report and urine), craving, signs and symptoms of opioid withdrawal, over-medication, adverse events, and concomitant medication taken since the last visit. During the final (fourth) week of the induction/stabilization period, all participants remained on a set daily dose of 8 mg, 16 mg or 24 mg of Suboxone®, as prescribed by the study physician. This study design assumed that the optimal dose for each participant was identified by the final week of the induction/stabilization period. Because determining the optimal dose was often

a dynamic process, we are aware that inadequate dosing may have been responsible for some dropout during the stabilization period.

Randomization to taper schedule—Upon completion of the induction/stabilization phase, participants were assigned randomly to either the 7-day or 28-day taper schedule. Randomization was stratified by maintenance dose at the end of the stabilization phase (8, 16 or 24 mg of Suboxone®), such that approximately equal numbers of participants on each dose were randomized to each taper schedule. Each treatment site had three sets of randomization cards (one set for each stabilization dose) prepared in advance. Based on stabilization dose, the top card in the appropriate stack was selected for the participant. This card listed the assigned taper schedule. On the day of randomization, the study physician gave the participant his/her medication, described the assigned taper schedule (7 or 28 days), provided explicit written instructions detailing exactly how to take the medication for the next seven days, including when and how to decrease dosage, and a clinic visit was scheduled for the next week. For each taper group, the stabilization dose determined the schedule for reducing dosage in the taper phase, designed to maximize participant comfort during the taper phase regardless of group assignment. Daily Suboxone® dosages for each taper group are shown in Table 1.

Data analysis

The objective of this research was to compare a short taper versus long taper following 4 weeks of Suboxone® medication stabilization. The primary study outcome was the percentage of participants in each taper condition who provided opioid-free urine specimens at the end of the taper and, as such, were considered successful in terms of withdrawal from study medication. Furthermore, data were collected at two follow-up points, enabling the tracking of participants within each taper group over time. Using a categorical variable eliminates the ability to look at reductions in opioid use, but our intent was to determine the percentage of participants who were able to avoid using opioids completely by the end of the taper schedule.

Secondary outcomes included differences in all drug use at the end of the taper, and comparisons of the groups at each follow-up time-point. Withdrawal and craving scores between groups were computed for baseline, the taper period, at the end of the taper and at both follow-up time-points. Analyses of concomitant medications addressed only those medications prescribed by a clinician to alleviate withdrawal symptoms.

Study procedures were identical across the two taper groups until the taper began, and the groups did not differ at baseline or through stabilization or at randomization in terms of demographic or drug use characteristics. Comparison of taper duration was the reason for the study, but length of taper was also seen as a potential confound. It is impossible to remove the effect of length of time when using a time-dependent variable. All efforts were made to equate study periods, study clinic visits and study follow-up time-points during the design of the study to remove any other possible confound.

One consideration was whether to present the data collected weekly during the taper period, rather than simply the end-of-taper data. This would compare results for 1 medication week and 3 non-medication weeks (for the 7-day group) to results for 4 medication weeks (for the 28-day group). Although the short taper group was instructed to return to clinic for weekly visits, the likelihood of this happening when no medication was being provided is reduced greatly compared to a group still receiving medication. Thus, comparing weekly data was deemed inappropriate. Similarly, the long taper group had medication to potentially alleviate any withdrawal symptoms that could lead to relapse, whereas the short taper group did not. While an argument could be made that the short taper group had less time to relapse and

hence would appear to do better, it could also be argued that the 28-day group had a longer period in which to adjust to abstinence and an opioid-free life-style.

Statistical methods include χ^2 tests to assess the differences between the taper groups for the primary outcome. Analysis of secondary outcomes, including analysis of withdrawal and craving at the start of the taper (randomization), at the end of taper, and at the 1-month and 3-month follow-ups, were conducted at discrete time-points using χ^2 and *t* tests as appropriate. All statistical tests utilized a two-tailed alpha level of $P < 0.05$.

RESULTS

Overview of outcomes by taper group

Typical of studies with multiple assessment time-points, the numbers of participants providing data decreased across time. At the end of the taper for the 7-day group 202 participants were present, of whom 113 were clean (44.31% of the randomized sample). For the 28-day taper group 172 participants were present at the end of the taper, and 78 were clean (29.89% of the randomized sample). The outcome of 'present and clean' refers to the number and percentage of participants who were present to provide a UA sample and who tested negative for opioids; percentage was computed based on the number randomized to each taper group. At the 1-month follow-up, 45 participants in the 7-day taper group who provided urine specimens (131) were clean (17.65% of the sample) and 46 participants in the 28-day taper group who provided urine specimens (123) were clean (17.62% of the sample). Finally, at the 3-month follow-up, of the 92 participants from the 7-day taper group who provided urine specimens 31 were clean (12.16%), and of the 114 participants from the 28-day group who provided urine specimens 35 were clean (13.41%).

Opioid-free at end of taper

Comparison of the 7-day ($n = 255$) and 28-day ($n = 261$) taper groups showed that the primary outcome (opioid-free urine test result at end of taper period) differed significantly by taper group ($\chi^2_{1,516} = 11.52$; $P = 0.0007$ $\phi = 0.150$), with a larger percentage of the 7-day group (44.3%) having an opioid-negative test result compared to the 28-day group (29.9%). Further analyses determined that gender ($\chi^2_1 = 0.16$; $P = 0.6875$; $\phi = -0.018$) and race ($\chi^2_6 = 8.29$; $P = 0.2122$ 0.05; $\phi = 0.127$) were not associated with differences in outcome.

Opioid abstinence at follow-ups

To assess whether outcome changed over time as a function of taper group, the percentages of participants in each taper group providing opioid-free urine samples were compared at the 1-month and 3-month follow-up assessments. As shown in Table 2, no statistically significant differences were found between the groups at either follow-up point.

Use of other drugs

Additional analyses examined urine test results for all drugs of abuse. Urine toxicology tests screened for amphetamines, barbiturates, benzodiazepines, cocaine, methamphetamine, phencyclidine (PCP), marijuana and tricyclic antidepressants. A group comparison of the percentages of drug-free participants at the end of the taper and the follow-up phases indicated that the groups did not differ significantly at any time-point (see Table 2).

Withdrawal and craving

The severity of withdrawal symptoms and craving was compared across groups at the end of taper, and at each follow-up point using multiple measures including the COWS, ARSW and one item from the VAS. At the end of taper, none of the withdrawal assessments was

significantly different between the two groups. At 1-month follow-up, the 7-day group (mean = 1.58; SD = 2.73) displayed greater withdrawal symptoms as measured clinically by the COWS, compared to the 28-day group [mean = 0.98; SD = 1.64; $t_{233} = 2.26$; $P = 0.0248$; confidence interval (CI): 0.08, 1.11], but there were no differences in self-reported withdrawal or craving. None of the withdrawal and craving assessments differed between the groups at the 3-month follow-up. Table 3 provides withdrawal and craving scores for each study time-point.

Concomitant medications

Analyses were conducted to examine differences between the taper groups in the number of medications used to treat withdrawal symptoms. Few participants reported using concomitant medications, with only 17 (7%) in the 7-day group and 26 (10%) in the 28-day group reporting any use during the period from randomization to the end of the taper. The most frequently used medications for both groups were over-the-counter non-narcotic analgesics such as ibuprofen, aspirin and acetaminophen. Other medications used to treat withdrawal symptoms included both over-the-counter and prescription formulations for nausea, diarrhea, insomnia and anxiety. Addressing only those who reported using concomitant medications during this period, the mean number of medications used by the 7-day group was 1.29 (SD = 0.69), with 1.54 (SD = 0.86) reported by the 28-day group (not significant).

Participant satisfaction

Participant satisfaction with the clinic, with the medication, and regarding treatment and recovery did not differ between the two taper groups for the taper period, at the end of the taper, or at the 1-month follow-up. The 28-day taper group, however, reported greater satisfaction at the 3-month follow-up (mean = 9.46, SD = 1.07) compared with the 7-day taper group (mean = 8.99, SD = 1.82; $t_{136} = -2.18$; $P = 0.0298$; CI: −0.8, −0.06).

DISCUSSION

Contrary to our hypothesis and contrary to the results from a previous study examining the effect of taper duration on outcome [22], the longer taper was not associated with better outcomes measured as opioid-free urine results collected at the end of the taper period. The results of the previous taper study showed that a slower taper resulted in better outcomes, whereas our results showed that the 7-day taper group had a greater percentage of opioid-free urine specimens collected at the end of the taper period compared with the 28-day group. Furthermore, the more rapid discontinuation of buprenorphine in the 7-day taper did not result in greater withdrawal symptoms or craving compared to the 28-day taper. The two taper groups did not differ in either self-reported or clinical assessments of withdrawal symptoms or self-reported craving. Although it is reasonable to predict that a more rapid detoxification would be associated with more discomfort, this expectation is not supported by the findings regarding concomitant medications. In fact, the 7-day taper group reported fewer medications used to address withdrawal symptoms than the 28-day taper group.

Although some physicians in the United States have begun to use buprenorphine in a more extended regimen for the management of opioid dependence, the eventual discontinuation of buprenorphine is a common treatment goal. There is little empirically derived information on how quickly this can be accomplished, and most clinicians opt intuitively for a longer, slower rate of taper. The current study provides empirical evidence supporting consideration of a short taper schedule [33].

This study was not intended to address whether clinicians should or should not take anyone off buprenorphine, nor was the use of buprenorphine in the stabilization phase of this protocol intended to be considered treatment. This study was also not intended to investigate the effectiveness of treatment with buprenorphine, but to provide some direction to clinicians who choose to take their patients off buprenorphine. The study reported here provides empirical information on the issue of whether a relatively short or long taper is associated with a better outcome, defined as an opioid-free urine specimen at the end of the taper period. Additionally, we wanted to examine whether taper schedule is related to withdrawal or elevated levels of craving—two uncomfortable conditions that could contribute to relapse. Relapse is common after detoxification and detoxification should be considered a transitional strategy. When patients are taken off buprenorphine, it is valuable to have some guidance on taper schedules in order to reduce the possibility of relapse and other negative outcomes.

The cost-effectiveness element of identifying optimal taper duration also is an important consideration. If patients do just as well (if not better) with a short taper in terms of relapse to illicit drug use and discomfort from withdrawal, then the cost savings of a short taper make it the logical choice, within the context of clinical appropriateness.

One consideration in designing this study was the matter of stabilization. There is a need to distinguish between pharmacological or physiological stabilization in contrast to clinical stabilization. The former is a matter of achieving a physiologically steady state, which is attainable over approximately five half-lives of the medication, occurring in 2–3 weeks. Clinical stabilization, on the other hand, refers to life changes achieved by patients and is much more variable and generally requires an appropriately longer time in treatment. The current study did not assess clinical stabilization.

Limitations of the study

Missing data—Our design identified the main outcome as ‘present and clean’ at the end of the medication period (i.e. opioid-free urine sample provided at the end of taper). This definition includes only opioid-free urine specimens as the target outcome, and avoids the issue of missing urine data because our analyses do not differentiate UA specimens that are not provided from those that are not opioid-free. This definition is similar to other research in which missing urine toxicology data are considered drug-positive UA results.

Program variation influences—A second limitation is due to the fact that the research was conducted within the context of real-world clinical settings. As such, we did not control for other potentially influential variables, such as variability in operations and ideology, or other program-specific factors that may influence outcomes.

Dropouts—Another issue typical in repeated-measures designs is that the number of participants assessed at each point declines over time. It is often assumed that participants who drop out or are not assessed at follow-up are doing poorly, although an argument may be made that dropouts may be doing well and, hence, find no need to remain in treatment or in a research study. In the current study, there were no differences in baseline characteristics of those who completed all study assessments with those who did not complete. The reduction in data points across assessment periods makes analyses complicated in determining which groups to compare. This is not likely to be an issue that will be resolved in the near future.

Conclusion

Results of this study have raised several issues requiring further research, but the findings provide useful information for clinicians prescribing buprenorphine to opioid-dependent individuals. With more clinicians using buprenorphine for the treatment of opioid dependence [14], it will become increasingly important to understand the advantages and disadvantages of buprenorphine administration methods, from induction to taper. Our findings indicate that a relatively quick taper may be advantageous and will not result in relapse to drug use at greater rates than among individuals given longer tapers. The findings of this study provide evidence that patients stabilized physiologically on a range of buprenorphine doses can be tapered successfully over 7 days and there is no advantage to prolonging the tapering schedule for weeks.

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Table 1

Suboxone® taper regimen for two study taper groups.

	Suboxone® dose (expressed as amount of buprenorphine)					
	7-day			28-day		
Stabilization dose	**8 mg**	**16 mg**	**24 mg**	**8 mg**	**16 mg**	**24 mg**
Study day						
1	8	16	24	8	16	24
2	6	12	20	8	16	24
3	6	10	16	6	12	20
4	4	8	12	6	12	20
5	4	4	8	6	12	20
6	2	2	4	6	10	16
7	2	2	2	6	10	16
8	–	–	–	6	10	16
9–11	–	–	–	6	8	12
12–14	–	–	–	4	8	10
15–16	–	–	–	4	6	8
17–19	–	–	–	4	4	6
20–22	–	–	–	2	4	4
23–25	–	–	–	2	2	2
26–28	–	–	–	2	2	2

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Table 2

Comparison of urine results by taper group and time-point (n = 516).

	Percentage of participants with drug-free UA (n)			
Time-point	**7-day (n = 255)**	**28-day (n = 261)**	**χ^2 value**	**P-value**
Opiates				
End of taper	44.31 (113)	29.89 (78)	11.52	*0.0007*
1-month follow-up	17.65 (45)	17.62 (46)	0.00	0.9946
3-month follow-up	12.16 (31)	13.41 (35)	0.18	0.6700
All drugs				
End of taper	24.71 (63)	18.77 (49)	2.67	0.1022
1-month follow-up	10.98 (28)	11.49 (30)	0.03	0.8534
3-month follow-up	6.67 (17)	9.20 (24)	1.13	0.2883

UA: urine analysis.

Table 3

Mean withdrawal and craving scores (standard deviation) for taper groups at assessment time-points.

	COWS		ARSW		VAS	
Assessment period	**7-day**	**28-day**	**7-day**	**28-day**	**7-day**	**28-day**
Baseline	8.68 (4.21)	8.30 (3.69)	62.69 (31.67)	61.66 (32.67)	71.15 (22.55)	68.15 (25.87)
Induction	5.01 (3.84)	4.49 (3.09)	41.06 (32.31)	37.27 (28.60)	46.73 (30.65)	44.33 (27.95)
Randomization	0.97 (1.38)	0.95 (1.24)	10.68 (16.03)	10.61 (15.52)	11.58 (18.99)	13.24 (19.97)
End of taper	2.73 (3.08)	2.53 (3.56)	21.93 (25.95)	17.96 (24.76)	24.50 (29.63)	23.24 (30.29)
1-month follow-up	1.58 (2.73)	0.98 (1.64)*	14.99 (23.26)	13.56 (19.50)	25.77 (30.61)	22.25 (28.49)
3-month follow-up	0.81 (1.65)	1.22 (1.77)	11.55 (21.41)	13.16 (17.76)	19.42 (27.54)	24.26 (29.52)

*$P < 0.05$. The withdrawal and craving scores presented from baseline to randomization are for all 516 randomized participants. Scores for end of taper through the 3-month follow-up time points decrease subsequently in numbers. COWS: Clinical Opiate Withdrawal Scale; ARSW: Adjective Rating Scale for Withdrawal; VAS: Visual Analog Scale.