A Randomized, Double-blind Evaluation of Buprenorphine Taper Duration in Primary Prescription Opioid Abusers

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IMPORTANCE Although abuse of prescription opioids (POs) is a significant public health problem, few experimental studies have investigated the treatment needs of this growing population.

OBJECTIVE To evaluate, following brief stabilization with a combination of buprenorphine hydrochloride and naloxone hydrochloride dihydrate, the relative efficacy of 1-, 2-, and 4-week buprenorphine tapering regimens and subsequent naltrexone hydrochloride therapy in PO-dependent outpatients.

DESIGN, SETTING, AND PARTICIPANTS A double-blind, 12-week randomized clinical trial was conducted in an outpatient research clinic. Following a brief period of buprenorphine stabilization, 70 PO-dependent adults were randomized to receive 1-, 2-, or 4-week tapers followed by naltrexone therapy.

INTERVENTION During phase 1 (weeks 1-5 after randomization), participants visited the clinic daily; during phase 2 (weeks 6-12), visits were reduced to thrice weekly. Participants received behavioral therapy and urine toxicology testing throughout the trial.

MAIN OUTCOMES AND MEASURES The percentage of participants negative for illicit opioid use, retention, naltrexone ingestion, and favorable treatment response (ie, retained in treatment, opioid abstinent, and receiving naltrexone at the end of the study).

RESULTS Opioid abstinence at the end of phase 1 was greater in the 4-week compared with the 2- and 1-week taper conditions (P = .02), with 63% (n = 14), 29% (n = 7), and 29% (n = 7) of participants abstinent in the 4-, 2-, and 1-week conditions, respectively. Abstinence at the end of phase 2 was also greater in the 4-week compared with the 2- and 1-week conditions (P = .03), with 50% (n = 11), 16% (n = 4), and 20% (n = 5) of participants abstinent in the 4-, 2-, and 1-week conditions, respectively. There were more treatment responders in the 4-week condition (P = .03), with 50% (n = 11), 17% (n = 4), and 21% (n = 5) of participants in the 4-, 2-, and 1-week groups considered responders at the end of treatment, respectively. Retention and naltrexone ingestion also were superior in the 4-week vs briefer tapers (both P = .04). Experimental condition (ie, taper duration) was the strongest predictor of treatment response, followed by buprenorphine stabilization dose.

CONCLUSIONS AND RELEVANCE This study represents a rigorous experimental evaluation of outpatient buprenorphine stabilization, brief taper, and naltrexone maintenance for treatment of PO dependence. Results suggest that a meaningful subset of PO-dependent outpatients may respond positively to a 4-week taper plus naltrexone maintenance intervention.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT00719095
Abuse of prescription opioids (POs), such as oxycodone, hydrocodone, and hydromorphone, is a significant US public health problem.\textsuperscript{1-4} Costs related to abuse of POs are estimated at $8 billion annually\textsuperscript{5,6} and include emergency department visits, overdoses, criminal activity, and psychiatric and medical consequences.\textsuperscript{1,7-10} Despite this, there is a dearth of empirical information regarding treatments for PO dependence.\textsuperscript{4,9,11} Generally, the most efficacious approach for treating opioid dependence involves maintenance treatment with agonist medications, such as methadone hydrochloride and buprenorphine hydrochloride.\textsuperscript{12-14} However, although agonist maintenance is the recommended treatment for most opioid-dependent patients, detoxification represents an important treatment option for several reasons.\textsuperscript{15,16} First, some opioid-dependent patients may prefer detoxification to extended maintenance.\textsuperscript{4,16-19} Second, access to maintenance treatment can be limited, especially in many rural areas that are struggling with high rates of PO abuse.\textsuperscript{20-24} Finally, some patients may possess demographic or drug use characteristics that are suggestive of lower baseline severity,\textsuperscript{25-28} which has been associated with favorable response to detoxification.\textsuperscript{29-31}

The aim of this double-blind, randomized clinical trial was to evaluate an outpatient detoxification treatment for PO-dependent adults. More specifically, following a brief period of stabilization with a combination of buprenorphine and naloxone hydrochloride dihydrate, the relative efficacy of 1-, 2-, and 4-week buprenorphine tapering regimens was examined. A recent review\textsuperscript{32} suggested a positive association between buprenorphine taper duration and treatment outcomes; however, there have been few prospective, parametric evaluations, and results of the existing studies have been mixed. Two studies,\textsuperscript{33,34} for example, found that a buprenorphine taper duration of approximately 1 month produced greater end-of-taper abstinence than did briefer durations. However, a larger-scale study\textsuperscript{35} reported that a 7-day taper produced better rates of opioid abstinence on the final day of treatment than did a 28-day taper, although no differences remained at 1- and 3-month follow-up. Taken together, there is broad consensus that more needs to be learned about how to taper buprenorphine to discontinuation without individuals resuming opioid use.

Methods

Participants

The study took place at an outpatient research clinic in Burlington, Vermont. Participants were recruited through newspapers and flyers between October 5, 2007, and November 4, 2009. Participants had to be aged 18 years or older, meet DSM-IV criteria for opioid dependence, provide an opioid-positive urinesample, be willing to undergo detoxification, report a PO as their primary drug of abuse, and be using the PO illicitly. Individuals requiring opioids for pain were excluded, as were those who were pregnant or nursing or had a significant and unstable psychiatric (eg, active psychosis) or medical (eg, acute cardiovascular disease) illness that could interfere with consent or participation. The study was approved by the local institutional review board, and participants provided written informed consent.

Study Design

The aim was to compare, following a brief stabilization period, 3 durations of buprenorphine taper in PO-dependent adults. Because detoxification is often associated with relapse,\textsuperscript{36} the tapering period was followed by maintenance on naltrexone hydrochloride, a competitive antagonist that blocks opioid reinforcement and reduces opioid use.\textsuperscript{37,38} All participants received individual behavioral therapy based on the Community Reinforcement Approach, which has been demonstrated as efficacious with alcohol-, cocaine-, and opioid-dependent outpatients.\textsuperscript{39-41}

Participants underwent a brief buprenorphine stabilization period and were then randomly assigned to a 1-, 2-, or 4-week taper (Figure 1). Stratification variables included stabilization dose, illicit opioid abstinence during stabilization, past-month cocaine use, sex, current alcohol dependence, and current chronic pain operationalized as (1) endorsement of the first question of the Brief Pain Inventory\textsuperscript{42} (ie, whether one has...
pain other than everyday kinds of pain) and (2) duration of pain longer than 3 months. During phase 1 (weeks 1-5 after randomization), participants visited the clinic daily; during phase 2 (weeks 6-12), visits were reduced to thrice weekly (Monday, Wednesday, and Friday). Withdrawal was assessed and adjuvant therapy with nonopioid medications (ie, clonidine hydrochloride, hydroxyzine hydrochloride, loperamide hydrochloride, and promethazine hydrochloride) was available at each visit. Participants provided staff-observed urine specimens thrice weekly.

**Measures**

The intake assessment included completion of a drug history, the substance dependence section of the DSM-IV, Addiction Severity Index, Beck Anxiety and Depression Inventories, Brief Pain Inventory, Michigan Alcoholism Screening Test, and Fagerström Test for Nicotine Dependence; medical screening; and a timeline followback assessment of past-month use of opioids and other drugs. Additional measures administered at each visit prior to dosing included timeline follow-back of opioid and other drug use since the last visit, completion of the Clinical Institute Narcotic Assessment of opioid withdrawal, and visual analog ratings of withdrawal and opioid effects.

**Drugs**

Medications were administered in a double-blind, double-dummy manner, with participants receiving sublingual tablets and capsules at each visit. Buprenorphine/naloxone and color-matched placebo were manufactured by Reckitt Benckiser Pharmaceuticals Inc and provided by the National Institute on Drug Abuse. Doses were prepared by the hospital’s investigational pharmacy and administered under research nurse observation. Participants received 5.5 sublingual tablets at each visit, containing a combination of active and/or placebo buprenorphine. Naltrexone (12.5, 25, 50, 100, and 150 mg) and placebo capsules (size 0, opaque hard gelatin) were prepared using naltrexone hydrochloride and powdered lactose. Participants ingested 3 capsules at each visit, containing a combination of active and/or placebo naltrexone. Participants and staff remained blinded to dose, taper duration, and the point at which naltrexone began.

**Procedure**

**Administration of Study Medications**

During stabilization, participants attended the clinic daily and withdrawal was assessed before study medication was administered. Individualized dose adjustments were determined using a Clinical Institute Narcotic Assessment–based protocol aimed at stabilizing participants on a dose sufficient to achieve withdrawal suppression without intoxication or sedation. Reductions during taper occurred in a graded fashion, with the stabilization dose reduced by 2-mg steps to 2 mg, followed by a 1-mg dose and placebo. Treatment in participants who underwent tapering without resuming opioid use was transitioned to naltrexone, with induction individually tailored to prevent withdrawal precipitation using minimum criteria of at least 1 opioid-negative urine sample and no self-reported opioid use in the prior 24 hours. Naltrexone treatment began with 12.5 mg on day 1, 25 mg on days 2 and 3, and 50 mg on day 4. Daily administration of 50 mg continued through phase 1, followed by thrice-weekly doses of 100, 100, and 150 mg during phase 2. Failure to transition to naltrexone by the end of phase 1 resulted in discharge from the study and referral to a local treatment program.

**Biochemical Testing**

Urine specimens were analyzed on site via enzyme-multiplied immunoassay (MGC 240; Microgenics) for opioids, methadone, buprenorphine, oxycodone, and propoxyphene. Randomly selected samples were analyzed once weekly for cocaine, amphetamines, benzodiazepines, marijuana, and barbiturates. Three consecutive missed urine specimens resulted in discharge. Breath alcohol levels were assessed at each visit (Alco-Sensor III; Intoximeters Inc).

**Behavioral Therapy**

The platform behavioral therapy was based on the Community Reinforcement Approach but was adapted for PO-dependent patients undergoing detoxification. Participants were offered twice-weekly 1- to 1.5-hour sessions with a master’s-level therapist. Topics included coping with withdrawal, human immunodeficiency virus and hepatitis education, relapse prevention, and developing recreational activities and social networks, with additional components tailored to an individual’s needs (eg, employment, education, health insurance, insomnia, depression, and anger management). Sessions were guided by a manual-based protocol; however, the therapist maintained a flexible approach toward appointment scheduling and goal setting and, although participants were encouraged to attend all scheduled therapy sessions, no punitive consequences were administered for missed sessions. Therapists received clinical supervision weekly.

**Statistical Analysis**

Primary analyses included all participants randomized consistent with an intent-to-treat approach to clinical trials. The study was designed to have sufficient power to detect an increasing trend in retention across the 3 taper conditions, corresponding to a 30% difference between 1- and 4-week conditions. The experimental groups were compared for differences in baseline demographics and other characteristics using analyses of variance for continuous variables and χ² tests for categorical variables. In addition, χ² tests were used to compare treatment conditions on the percentage of participants abstinent at the end of phases 1 (weeks 1-5) and 2 (weeks 6-12), as well as conditions on treatment retention and naltrexone ingestion. Abstinence was defined as a urine specimen biochemically verified to be opioid negative. Buprenorphine-positive results during phase 1 were not considered illicit opioid positive, but any positive specimen during phase 2 was considered positive for illicit opioid use. A favorable treatment response was defined as being retained in treatment, being opioid abstinent, and receiving naltrexone at the end of the study. Stepwise logistic regression was used to examine
predictors of treatment response considering treatment condition and participant characteristics as potential covariates. Statistical analyses were performed using commercial software (SAS, version 9.3; SAS Institute Inc). Statistical significance was determined using \( \alpha = .05 \).

**Results**

**Participants**

Ninety-one individuals were screened, with 70 participants randomly assigned to the 1-week (n = 24), 2-week (n = 24), or 4-week (n = 22) tapering regimens (Figure 2). There were no significant differences between treatment conditions in baseline characteristics (Supplement [eTable]). Mean (range) duration of the stabilization phase and dose were 14.2 (8-20) days and 11.5 mg (2-20 mg), respectively; these did not differ significantly between experimental conditions.

**Opioid Abstinence**

There was a significant effect of taper duration on opioid abstinence in phase 1 \( (P = .02) \). At the final visit of phase 1, 63% (n = 14), 29% (n = 7), and 29% (n = 7) of participants were abstinent in the 4-, 2-, and 1-week conditions, respectively (Figure 3). A significantly greater percentage of participants were abstinent in the 4-week compared with the 1- and 2-week conditions. A similar effect was seen in phase 2 \( (P = .03) \), with 50% (n = 11), 16% (n = 4), and 20% (n = 5) of participants in the 4-, 2-, and 1-week conditions abstinent at the final visit and significantly better outcomes in the 4- vs 1- or 2-week conditions. When percentage of opioid-negative specimens was collapsed across all study visits, the percentage of negative

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**Figure 2. Consolidated Standards for Reporting of Trials Flow Diagram of Participants**

A schematic of participant enrollment, randomization, and study completion.

**Figure 3. Effects of Buprenorphine Taper Duration on Illicit Opioid Abstinence Achieved**

Data points represent the percentage of opioid-negative urine samples submitted at each consecutive urine-sample visit before and after randomization. Data are presented for the entire group of participants at intake and stabilization and for each experimental group after randomization: 1-week, 2-week, and 4-week taper conditions.
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Original Investigation Research

Retirement

When retention was examined in phase 1, 64% (n=14), 29% (n=7), and 42% (n=10) of patients in the 4-, 2-, and 1-week conditions were retained through week 5, respectively (P=.06) (Figure 4). A significant effect of taper duration was seen in phase 2 (P=.04), with 50% (n=11), 21% (n=4), and 21% (n=6) of participants assigned to the 4-, 2-, and 1-week conditions still receiving naltrexone at the final visit (Figure 4). A significantly greater percentage of participants in the 4- vs 2-week condition were still receiving naltrexone at the end of the study.

Naltrexone Ingestion

There was a significant effect of taper duration on naltrexone ingestion at the end of phase 2 (P=.04), with 50%, 17%, and 25% of participants in the 4-, 2-, and 1-week conditions still receiving naltrexone at the final visit (Figure 4). A significantly greater percentage of participants in the 4- vs 2-week condition were still receiving naltrexone at the end of the study.

Predictors of Favorable Treatment Response

Multivariate analyses were conducted to identify baseline participant characteristics associated with favorable treatment response. When participants were dichotomized on the basis of treatment response, there were significantly more treatment responders in the 4-week condition (P=.03), with 50% (n=11), 17% (n=4), and 21% (n=5) of participants assigned to the 4-, 2-, and 1-week conditions considered responders at the end of treatment, respectively. In analyses that considered experimental condition and stratification variables as potential predictors of treatment response, taper duration and stabilization dose met the entry criteria (P<.05). Participants assigned to the 4-week taper had an estimated 4-fold greater odds of a favorable treatment response compared with those in the 1-week taper (odds ratio [OR], 4.1; 95% CI, 1.1-16.0; P=.04) and nearly 6 times compared with the 2-week condition (5.9; 1.4-24.7; P=.01). The only covariate that met criteria for entry was patients' stabilization dose, with doses of 8 mg or greater being associated with decreased odds of a favorable treatment response (OR, 0.26; 95% CI, 0.08-0.90; P=.03).

Discussion

The aim of this randomized, double-blind trial was to evaluate, following a brief stabilization period, the relative efficacy of 1-, 2-, and 4-week buprenorphine tapering regimens and subsequent naltrexone therapy for PO-dependent adults. The 4-week taper produced superior outcomes over briefer durations, with 50% of participants retained, abstinent, and receiving naltrexone at the end of the study compared with 17% and 21% for the 2- and 1-week groups, respectively. These results suggest that the duration of taper influences treatment outcome and are consistent with prior studies showing favorable outcomes with longer- vs briefer-duration detoxification.

The amounts of abstinence achieved in the present study are generally greater than those seen in prior studies of outpatient opioid detoxification, including a recently completed National Institute on Drug Abuse Clinical Trials Network trial that sought to evaluate the efficacy of brief and extended buprenorphine treatment for PO abusers. In that study, which is, to our knowledge, the only other to prospectively evaluate outpatient buprenorphine detoxification for PO abusers, only 6% to 9% of the participants remained abstinent following a 2-week taper. Several factors may contribute to these differences. First, our behavioral therapy was more intensive than the counseling used in the Clinical Trials Network trial and could have contributed to the favorable outcomes. It is impossible to disentangle the contribution of the counseling component to outcomes. Second, the inclusion of naltrexone therapy could have helped prevent resumption of illicit opioid use following detoxification. Third, we used a double-blind, double-dummy design wherein neither participants nor staff knew the doses received, the duration of taper, or the point at which naltrexone therapy began. Although this permitted rigorous evaluation of outpatient buprenorphine detoxification for PO dependence, it is possible that remaining blinded to one’s medication status could help facilitate outcomes. We know of no empirical data demonstrating more favorable outcomes under blinded vs nonblinded tapering conditions. Furthermore, because all participants received double-blind medication administration, this would not explain the differential treatment response across conditions. In addition, the differential outcomes are not likely the result of differences in patient characteristics. For example, participants in the present study and the Clinical Trials Network study were largely similar in age (28 vs 33 years), sex (69% vs 60% male), race (94% vs 91% white), educational level (12 vs 13 years), employment (63% vs 64% full-time), duration of opioid use (5 vs 5 years), and past-month frequency of opioid use (26 vs 28 days).

The finding of superior outcomes with longer vs briefer detoxification is inconsistent with results from a Clinical Trials Network trial conducted by Jing et al in which opioid-dependent patients were randomized to a 7- or 28-day buprenorphine tapering regimen. In that study, 44% of the 7-day
group was abstinent at the end of taper compared with 30% of the 28-day group. These differences were no longer evident after the taper, with 17% and 13% of participants abstinent at 1- and 3-month follow-up, respectively. There were numerous differences between the present study and that trial. Participants in the Ling et al trial were older than our sample and were primary heroin abusers. In addition, that study was open label, with a 4-week stabilization period and no naltrexone component. Intensity of treatment was lower, with participants attending the clinic only weekly and encouraged to participate in a standard psychosocial program that varied across study sites. Finally, the 2 trials differed in how the abstinence outcome was calculated. In the present study, taper conditions were compared on the percentage of participants abstinent at a consistent time point (ie, end of weeks 5 and 12). In the Ling et al study, the percentage of participants abstinent was calculated from 2 different time points (ie, end of week 1 for the 7-day group vs end of week 4 for the 28-day group). The extent to which these differences may account for the differential outcomes is unknown, but the differences are important to consider when comparing findings.

When predictors of treatment response were examined, taper duration was the strongest predictor, followed by stabilization dose. Given that lower stabilization doses reflect lower physiologic dependence, this finding of lower baseline severity predicting favorable treatment response is consistent with the larger literature. Several other aspects of our results also are consistent with earlier studies. First, prior reports have noted that at least a subset of PO-dependent patients may be young, have less severe opioid and other drug use, have less use of the intravenous route, and have greater psychosocial stability. The mean age in our study was 27 years, with 35 participants (49%) aged 25 or younger. Although all participants were opioid dependent, most reported their primary route of administration as intranasal and their daily doses as moderate. Participants also had a relatively high rate of employment and educational level and few medical or psychiatric problems. Second, an earlier report suggested that PO abusers may express less interest in methadone maintenance than in other forms of treatment. Our patients were asked at intake to rate their interest in methadone maintenance, buprenorphine maintenance, and buprenorphine detoxification on a visual analog scale that ranged from 0 (not at all) to 100 (extremely). Mean ratings of these modalities were 46.5, 70.3, and 70.8, respectively, providing some evidence that at least a subset of PO-dependent individuals may be unwilling to seek methadone maintenance. Finally, access to agonist maintenance can be limited in many geographic regions, particularly in areas where PO dependence is common. For example, although rates of PO abuse in Vermont are among the highest in the country, there remains a lengthy waiting list for access to our state’s primary methadone service. Taken together, our data support the importance of exploring whether some PO-dependent patients may achieve favorable outcomes without extended agonist maintenance. However, although these data suggest that a meaningful subset of PO-dependent patients may do well with a carefully implemented buprenorphine detoxification regimen, ongoing antagonist therapy and other services will likely be important for longer-term success. To the extent that naltrexone helped prevent relapse in the present study, recently developed sustained-release naltrexone formulations could provide ongoing pharmacologic support following detoxification.

Several potential limitations of the study relate to the generalizability of our sample to the larger population of PO-dependent treatment seekers. Participants were primarily white and reported oxycodone as their primary drug of abuse, both of which may limit the generalizability of our results to the larger population of PO abusers. However, most PO users are white and oxycodone is one of the most commonly abused POs. Patients requiring opioids for pain also were excluded, although it seems reasonable to expect that PO-dependent individuals with significant or chronic pain are not likely to be candidates for detoxification and naltrexone. Our sample was not a “pure” PO-dependent population in that we did not exclude individuals with a history of heroin use. However, our definition of primary PO abusers is consistent with that of several prior studies in this population. Participants also exhibited a clear predominance of PO use, with all identifying a PO as their primary drug of abuse and only 1 of 70 identifying heroin as their secondary opioid. Furthermore, although approximately half of the participants reported ever using heroin, only 3% had used heroin on 5 or more days in the month prior to intake.

Several potential limitations also relate to our study design. Although this study offers a rigorous evaluation of buprenorphine taper duration and naltrexone maintenance in PO-dependent patients, there was no effort to isolate the effects of the behavioral therapy. Thus, the contribution of the Community Reinforcement Approach to outcomes is unknown. We also did not include a comparison group receiving buprenorphine maintenance, and inclusion of such a group would have permitted a comparison of outcomes associated with brief buprenorphine taper vs continued administration. However, scientific and clinical evidence generally show that extended agonist maintenance produces favorable outcomes compared with detoxification. In this study, we simply sought to develop and evaluate a protocol that might produce good outcomes for patients for whom detoxification is potentially appropriate or for whom extended agonist maintenance is undesirable or unavailable. In addition, our ability to document abstinence was influenced by retention, which differed as a function of experimental condition. Further studies could aim to disentangle abstinence and retention, perhaps by offering financial incentives contingent on study completion (but independent of urinalysis results). Finally, stabilization was brief, with a mean duration of 14.2 days. Although its duration was individualized and sufficient to achieve an 82% rate of illicit opioid abstinence among participants prior to randomization, a longer duration might have produced greater stabilization in other areas of psychosocial functioning. To our knowledge, the contribution of the duration of stabilization preceding the taper regimen has not been empirically evaluated. Further investigation of this parameter could inform future efforts to develop more efficacious detoxification strategies.
Finally, several possible limitations relate to the generality of our findings to routine clinical practice. First, all 3 taper durations were shorter than those often used in outpatient clinical settings. Comparison of the 4-week taper with longer durations would be of scientific and clinical interest. Second, the frequency of patient visits exceeded that often used in office-based practices. The degree to which this contributed to outcomes is unknown; the clinical support and oversight needed for successful detoxification may be more compatible with a specialized outpatient treatment program than routine clinical practice in an office-based setting. Third, our taper schedule included a 1-mg dose. It may be common practice for physicians to have their patients split their doses to achieve the prescribed dose; however, there are no federal or manufacturer guidelines supporting this practice. Finally, access to agonist maintenance is more limited in Vermont than in some other geographic regions. Whether this influenced our treatment outcomes is unknown but may also be an important consideration when comparing across studies on this topic.

Taken together, this study provides a rigorous experimental investigation of the treatment needs of the growing population of PO-dependent adults. Our results suggest that a subset of PO abusers may respond favorably to a brief but carefully crafted outpatient treatment involving buprenorphine detoxification, naltrexone maintenance, and behavioral therapy. Additional controlled studies are needed to better understand the parameters of efficacious treatments for PO dependence, as well as to identify the individuals for whom brief vs longer-term treatments are warranted. Overall, this new information will inform efforts to develop efficacious treatments for the growing problem of PO dependence.

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