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Primary Care-Based Buprenorphine Taper vs Maintenance Therapy for Prescription Opioid Dependence:

A Randomized Clinical Trial

David A. Fiellin, MD, **Richard S. Schottenfeld, MD**, **Christopher J. Cutter, PhD**, **Brent A. Moore, PhD**, **Declan T. Barry, PhD**, and **Patrick G. O'Connor, MD, MPH**

Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut (Fiellin, Cutter, O'Connor); Department of Psychiatry, Yale University School of Medicine, New Haven, Connecticut (Schottenfeld, Moore, Barry).

Abstract

IMPORTANCE—Prescription opioid dependence is increasing and creates a significant public health burden, but primary care physicians lack evidence-based guidelines to decide between tapering doses followed by discontinuation of buprenorphine hydrochloride and naloxone hydrochloride therapy (hereinafter referred to as buprenorphine therapy) or ongoing maintenance therapy.

OBJECTIVE—To determine the efficacy of buprenorphine taper vs ongoing maintenance therapy in primary care–based treatment for prescription opioid dependence.

DESIGN, SETTING, AND PARTICIPANTS—We conducted a 14-week randomized clinical trial that enrolled 113 patients with prescription opioid dependence from February 17, 2009, through February 1, 2013, in a single primary care site.

INTERVENTIONS—Patients were randomized to buprenorphine taper (taper condition) or ongoing buprenorphine maintenance therapy (maintenance condition). The buprenorphine taper was initiated after 6 weeks of stabilization, lasted for 3 weeks, and included medications for opioid withdrawal, after which patients were offered naltrexone treatment. The maintenance group

Corresponding Author: David A. Fiellin, MD, Department of Internal Medicine, Yale University School of Medicine, 367 Cedar St, PO Box 208093, New Haven, CT 06520 (david.fiellin@yale.edu).

Author Contributions: Drs Fiellin and Moore had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Fiellin, Schottenfeld, Moore, Barry, O'Connor.

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Critical revision of the manuscript for important intellectual content: Fiellin, Schottenfeld, Cutter, Barry, O'Connor.

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received ongoing buprenorphine therapy. All patients received physician and nurse support and drug counseling.

MAIN OUTCOMES AND MEASURES—Illicit opioid use via results of urinanalysis and patient report, treatment retention, and reinitiation of buprenorphine therapy (taper group only).

RESULTS—During the trial, the mean percentage of urine samples negative for opioids was lower for patients in the taper group (35.2% [95% CI, 26.2%−44.2%]) compared with those in the maintenance group (53.2% [95% CI, 44.3%−62.0%]). Patients in the taper group reported more days per week of illicit opioid use than those in the maintenance group once they were no longer receiving buprenorphine (mean use, 1.27 [95% CI, 0.60–1.94] vs 0.47 [95% CI,0.19–0.74] days). Patients in the taper group had fewer maximum consecutive weeks of opioid abstinence compared with those in the maintenance group (mean abstinence, 2.70 [95% CI, 1.72–3.75] vs 5.20 [95% CI, 4.16–6.20] weeks). Patients in the taper group were less likely to complete the trial (6 of 57 [11%] vs 37 of 56 [66%]; $P < .001$). Sixteen patients in the taper group reinitiated buprenorphine treatment after the taper owing to relapse.

CONCLUSIONS AND RELEVANCE—Tapering is less efficacious than ongoing maintenance treatment in patients with prescription opioid dependence who receive buprenorphine therapy in primary care.

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Prescription opioids are the second most commonly abused of all drug classes in the United States, affecting an estimated 4.8 million individuals and contributing to the recent increase in opioid dependence and drug overdose.[1] Overdose is now a leading cause of accidental death in the United States, with most deaths due to prescription opioids.[2,3]

Treatment options for prescription opioid dependence include primary care- and office-based buprenorphine hydrochloride and naloxone hydrochloride (hereinafter referred to as buprenorphine therapy), and an estimated 600 000 individuals received this treatment through 2009.[4] General practice and family medicine physicians are the most common prescribers of buprenorphine, and organizations such as the American College of Physicians encourage physician education about the treatment of prescription opioid dependence and the development of evidence-based treatment strategies.[3,5,6] Physicians and patients routinely decide between pharmacologically assisted withdrawal (detoxification or taper) and ongoing maintenance treatment, but limited research data are available to guide these decisions. Although earlier studies with heroin-dependent patients demonstrated improved outcomes with methadone maintenance therapy compared with methadone taper[7,8] and decreased mortality, risk for human immunodeficiency virus transmission, and criminal behavior,[9–12] patients with prescription opioid dependence can differ in important regards from heroin-dependent patients–often having shorter histories of opioid dependence, lower levels of physical dependence, better occupational and social functioning, and improved treatment outcomes[13–16]–leading to questions about whether prescription opioid–dependent patients require ongoing maintenance treatment or might instead benefit even more from shorter-term taper followed by continued counseling and treatment with the opioid antagonist, naltrexone. In addition, buprenorphine taper may be better tolerated than

methadone taper because of buprenorphine's partial agonist properties and persistence at the opioid μ receptor.[17–19]

In practice, patients often request and receive medication taper instead of maintenance therapy, and office-based physicians may be enthusiastic to provide tapers because this method allows them to treat more patients, fits with what many patients request, and could reduce the need for long-term opioid therapy.[20–22] Most evaluations of physicians prescribing buprenorphine indicate that many provide taper and maintenance treatments.[20,23,24] In one survey, 51% of physicians indicated that they provided taper and maintenance therapy and 8% provided only taper.[24] To provide data that could be used to develop evidence-based guidelines regarding buprenorphine taper or maintenance treatment for patients dependent on prescription opioids, we conducted a randomized clinical trial comparing buprenorphine taper and maintenance treatment in a heterogeneous population of patients with prescription opioid dependence in a primary care setting.

Methods

Design Overview

We conducted a single-site, open-label randomized clinical trial. The 18-week study consisted of 2 weeks of induction and stabilization of buprenorphine therapy, 14 weeks of the trial, and 2 weeks of continuing clinical care after trial completion, during which referrals to ongoing treatment were made. The study was approved by the human investigation committee of Yale University School of Medicine. Written informed consent was obtained from all patients.

Setting and Participants

Patients were treated at the Primary Care Center of Yale–New Haven Hospital, which provides no specialty addiction treatment other than buprenorphine therapy. All patients underwent assessment for eligibility by research assistants who did not participate in treatment allocation. Study identification numbers were assigned to eligible patients. All enrolled patients met criteria for prescription opioid dependence according to the *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition, Text Revision) (*DSM-IV-TR*).[25] Patients were excluded if they met *DSM-IV-TR* criteria for current dependence on alcohol, benzodiazepines, or cocaine; were unwilling to undergo randomization; had a history of heroin dependence or injection drug use; used heroin as their primary opioid in the past 3 months; had undergone prior methadone maintenance treatment; required opioids for a pain-related diagnosis; were a current suicide or homicide risk; had a current psychotic disorder or untreated major depression; were unable to comprehend English; or had life-threatening or unstable medical problems. Women of childbearing age agreed to contraception and monthly pregnancy monitoring. Study enrollment occurred from February 17, 2009, through February 1, 2013. The CONSORT diagram in Figure 1 shows participant flow through the phases of the study.

Buprenorphine

We used a tablet formulation of buprenorphine hydrochloride and naloxone hydrochloride in a 4:1 ratio. For all patients, treatment started with a 2-week induction and stabilization period (mean [SD], 12 [2.9] [95% CI, 11.5–12.5] days), during which patients underwent evaluation and education by nurses during brief (5- to 10-minute) sessions, thrice weekly. After the first 2 weeks, patient medications were dispensed weekly. The target induction and stabilization dose was 16 mg/d of buprenorphine hydrochloride, although lower doses were offered based on an assessment of patient need and desire. The mean (SD) dose of buprenorphine hydrochloride during the induction and stabilization phase was 15.0 (3.0) mg/d and did not differ significantly between treatment groups ($P = .34$).

Randomization

After the induction and stabilization period, patients were randomly assigned in a 1:1 ratio to receive taper or maintenance therapy (each described below). An urn randomization procedure[26] under the control of an investigator (B.A.M.) who was not involved with enrollment or assessment for eligibility was used to ensure that the groups were similar with regard to current cocaine abuse[25] and urine samples with findings negative for opioids and cocaine at the time of randomization. Treatment allocation was communicated by an investigator not involved in assessment for eligibility or randomization who notified each patient of his or her treatment assignment in a sequential manner.

Interventions

Patients randomized to the taper condition received a stable dosage of buprenorphine hydrochloride for an additional 4 weeks after randomization followed by a gradual taper (2-mg decrease every 3 days) for 3 weeks. Patients in the taper group were provided prescriptions to use for opioid withdrawal symptoms (nonsteroidal anti-inflammatory medication, an anti-emetic, a sleeping aid, and clonidine hydrochloride). Patients in the taper group who achieved 7 days or more of opioid abstinence after their last dose of buprenorphine were also offered oral naltrexone (25 mg on day 1, followed by 50 mg/d) along with ongoing clinical care and counseling (see below) for the remainder of the trial. The availability of injectable depot naltrexone was also discussed with these patients. Patients randomized to the maintenance condition received buprenorphine at their induction and a stabilization dose for 14 weeks, with an option for successive increases in the buprenorphine hydrochloride dosage to 20 and 24 mg/d depending on patient comfort or evidence of ongoing (for 3 successive weeks) illicit opioid use.

Clinical Care and Counseling

All patients received ongoing care from physicians, nurses, and drug counselors for the duration of the 14-week trial phase. Primary care physicians (including D.A.F. and P.G.O.) who had training in addiction medicine provided physician management to all patients during brief, 15- to 20-minute visits. These visits were scheduled weekly for the first 2 weeks, every 2 weeks for the next 4 weeks, then monthly. The content of these medically focused visits targeted supporting abstinence and has been described in detail previously.[27,28] For patients in the taper condition, physician management included discussion of

management of opioid withdrawal symptoms and overdose risk. Nurse counseling, as previously described, was provided to all patients during weekly 20- to 30-minute sessions.[27] In addition, all patients received weekly onsite drug counseling focused on education about drug use, drug dependence, and relapse prevention in 45-minute sessions by doctoral or master's level clinicians (including C.J.C. and D.T.B.).[29–31] To assist with symptom management and challenges to relapse during and after the medication taper for patients in the taper condition, nurse counseling and drug counseling tailored to manage withdrawal symptoms and achievement and maintenance of abstinence were offered more frequently (≤2 additional 20-minute sessions per week each) during and after the period of medication tapering.

Protective Transfer and Treatment Termination

In the case of persistent relapse (unremitting illicit opioid use, defined as ≥2 consecutive weeks of daily illicit opioid use and opioid-positive urine samples) after completion of the first 6 weeks of the study, patients were considered to have met criteria for protective transfer. Data from patients who met criteria for protective transfer were censored as of the date of the transfer. A study physician worked with participants who met criteria for protective transfer to identify a clinically appropriate treatment plan (eg, referral for methadone maintenance therapy, inpatient or intensive outpatient treatment, or, for participants assigned to buprenorphine taper, resuming buprenorphine therapy using the same induction procedure as initially). We informed all participants at the time of study enrollment about the protective transfer provisions in the study. We did not specifically inform participants in advance that reinitiating buprenorphine therapy could be an option, to give the tapering strategy the best likelihood of success and avoid inadvertently encouraging participants to relapse (eg, to avoid patients purposefully relapsing in an effort to have buprenorphine therapy restarted). All urine samples collected from patients in the taper group after completion of their taper were tested for buprenorphine, and we considered a test result positive for buprenorphine to be positive for opioids when determining criteria for protective transfer. Patients who missed 1 week of maintenance medications or 3 successive sessions of physician management had their treatment terminated and were offered referral to other treatment providers.

Outcomes

Illicit opioid use was measured weekly by urinalysis and patient-reported frequency of drug use using a 7-day timeline followback method.[32] The primary a priori outcome measures were the overall percentage of opioid-negative urine samples, patient-reported days per week of illicit opioid use, and patient-reported maximum consecutive weeks of abstinence from illicit opioids. The maximum consecutive weeks of abstinence was calculated as the longest number of consecutive weeks of documented abstinence without missing data. Secondary out comes included the percentage of patients meeting criteria for protective transfer and treatment retention (number of days from randomization to last clinical contact). Outcomes specific to the taper condition were the percentage of patients initiating naltrexone therapy and the percentage requiring reinitiation of buprenorphine treatment owing to unremitting illicit opioid use. Urine samples were analyzed using a semiquantitative homogeneous

enzyme immunoassay for opioids, oxyco-done, methadone, and buprenorphine (for urine samples after taper only).

Statistical Analysis

On the basis of prior work,[7,16] we anticipated an effect size (Cohen *d* statistic[33]) of 0.55 in the percentage of opioid-negative urine samples, favoring maintenance over taper, which led to a planned sample size of 120 patients to account for attrition. We enrolled 113 of the planned 120 patients. Enrollment was terminated owing to fiscal and time constraints.

The patients' characteristics at enrollment were compared between the 2 groups with the use of the χ^2 test and analysis of variance, as appropriate. Analyses were planned in advance and were based on the intention-to-treat principle.

The mean percentages of opioid-negative urine samples and the maximum consecutive weeks of opioid abstinence were analyzed using the independent *t* test, with linear mixed models used to evaluate post hoc differences over time. Repeated-measures Poisson regression using generalized estimating equations with an autoregressive 1-correlation structure was used to evaluate treatment, time, and treatment × time effects for patient-reported days per week of il licit opioid use after randomization. The linear mixed models and generalized estimating equation procedures are adept at handling missing data and allow for intraparticipant serial correlation and unequal variance and covariance structure across time.[34–38] The percentage of patients remaining in the study was evaluated using the χ^2 test, and the number of trial days completed was evaluated with the use of the Kaplan-Meier product-limit method and the log-rank test. One interim analysis was conducted for safety, not efficacy, 6 months after 30 patients had been randomized to each of the 2 treatment conditions. This analysis determined that the percentage of patients meeting criteria for protective transfer did not differ ($P \geq .05$) between the 2 treatment conditions. All efficacy analyses involved 2-tailed tests of significance and were performed with the use of commercially available software (SPSS, version 19; IBM-SPSS). We considered $P < .05$ to be statistically significant.

Results

Demographic and Clinical Characteristics

The baseline demographic and clinical characteristics of the 113 patients who were randomized to the taper (n = 57) and maintenance (n = 56) conditions (Figure 1) are presented in the Table. Patients randomized to the taper condition reported fewer days of alcohol use in the past 30 days than those randomized to the maintenance condition ($P = .01$); no other significant baseline differences between treatment groups were observed.

Completeness of Urinalysis and Self-reported Data

The results of the urinalysis are based on 1062 samples of the 1582 total possible samples anticipated (67.1%) had all patients remained in treatment during the entire 14-week trial and provided all planned samples. Patients in the taper group provided fewer urine samples than those in the maintenance group (57.3% vs 78.2%; $P = .001$). The results regarding the

patient-reported frequency of illicit opioid use are based on 1044 assessments of the 1582 total possible assessments (66.0%) had all patients remained in treatment for the entire 14-week trial. Patients in the taper group completed fewer patient-reported assessments than those in the maintenance group (56.9% vs 76.3%; $P < .001$). To assess the correlation between urinalysis results and patient-reported abstinence, we examined the percentage of opioid-negative urine samples collected when the patient reported no illicit opioid use in the past 7 days. The percentage of opioid-negative urine samples in the setting of patient-reported abstinence was lower for the taper group (273 of 366 samples [74.6%]) than for the maintenance group (405 of 496 samples [81.7%]) ($P = .04$).

Illicit Drug Use Outcomes

Patients assigned to the taper condition had a lower overall mean percentage of opioid-negative urine samples (35.2% [95% CI, 26.2%−44.2%]) compared with those assigned to the maintenance condition (53.2% [95% CI, 44.3%−62.0%]). Post hoc analysis using linear mixed models evaluating urine samples over time indicated that patients in the taper and maintenance conditions had similar mean percentages of opioid-negative urine samples during the first 7 weeks of the trial while all patients were receiving medication (45.5% [95% CI, 32.0%−55.0%] vs 49.2% [95% CI, 39.9%−58.6%]) but differed during the last 7 weeks, when patients in the taper group were no longer receiving buprenorphine (33.2% [95% CI, 22.1%−44.2%] vs 64.2% [95% CI, 54.3%−74.1%]).

Mean patient-reported days per week of illicit opioid use differed by treatment condition over time ($P = .02$). Post hoc analyses indicated that during the first 7 weeks of the trial, patients in the taper and maintenance conditions reported a similar mean number of days per week of illicit opioid use (1.08 [95% CI, 0.67–1.49] vs 0.97 [95% CI, 0.58–1.36] days), but differed during the last 7 weeks (1.27 [95% CI, 0.60–1.94] vs 0.47 [95% CI, 0.19–0.74] days). Patients assigned to the taper condition achieved fewer mean maximum consecutive weeks of opioid abstinence than those assigned to the maintenance condition (mean abstinence, 2.70 [95% CI, 1.72–3.75] vs 5.20 [95% CI, 4.16–6.20] weeks).

Persistent Relapse and Treatment Retention

Patients in the taper group were more likely to require protective transfer (16 of 57 [28%] vs 3 of 56 [5%]; $P = .001$). The mean number of days retained in the trial was lower for patients in the taper group than the maintenance group (57.5 [95% CI, 47.0–59.9] vs 98.7 [95% CI, 88.0–109.4] days; $P < .001$) (Figure 2). Patients in the taper group were less likely to complete the 14-week trial (6 of 57 [11%] vs 37 of 56 [66%]; $P < .001$). In outcomes specific to the taper condition, 2 patients (4%) accepted prescriptions for naltrexone, and 16 patients (28%) had reinitiation of buprenorphine therapy.

Discussion

We investigated the use of buprenorphine taper vs maintenance therapy in primary care–based treatment of prescription opioid dependence. Buprenorphine taper resulted in fewer opioid-negative urine samples, more days of illicit opioid use, fewer weeks of continuous abstinence, and poorer retention in treatment. Very few patients undergoing buprenorphine

taper initiated naltrexone therapy or completed treatment, and 28% required reinitiation of buprenorphine therapy owing to relapse after the taper.

The findings of the present study supporting the superiority of buprenorphine maintenance therapy compared with taper for patients with prescription opioid dependence are consistent with and complement the findings from 2 prior studies[15,39] despite differences in study design and eligibility criteria. In contrast to one of these prior studies,[39] none of the patients in the present study had the buprenorphine taper initiated from the outset; we excluded patients whose pain required opioid analgesics; we offered naltrexone in the taper treatment plan; and all counseling and medication treatment were provided in a primary care office–based setting. In contrast to the other study,[15] we excluded patients with a history of heroin dependence or methadone maintenance therapy or individuals who had used heroin as their primary opioid in the past 3 months. In addition, patients in the present study were treated in primary care according to a schedule that is consistent with a generalist setting, and we used an open-label design to better facilitate support during tapering and buprenorphine doses that are available by prescription. Nonetheless, our study supports the primary finding from the prior 2 studies[15,39] and those examining metha done and buprenorphine treatment in heroin-dependent individuals, that illicit opioid use decreases while patients receive opioid agonist medication and increases with discontinuation of medication therapy.[7,8,15,39–41] The outcomes with buprenorphine taper were less positive in our study than in a prior study,[15] possibly owing to the intensive visit schedule in the previous study (daily patient visits for the first 5 weeks), which may have proved therapeutic or selected for individuals with an improved likelihood of benefitting from a taper.

Our study has limitations. To maximize the likelihood of treatment success with a buprenorphine taper and to select patients who were appropriate for management in primary care, we made a number of decisions regarding study eligibility criteria and treatment design. We excluded patients who had comorbid alcohol or cocaine dependence. Our physicians had more experience with buprenorphine and addiction medicine than most primary care providers. Similarly, on-site drug counseling is not routinely available in primary care settings. We chose a fixed taper schedule after a period of brief treatment to provide an opportunity for stabilization before the taper. The patient’s response to buprenorphine treatment did not affect treatment allocation. Alternative trial designs that restrict taper eligibility to those with a period of documented abstinence might yield different results. We did not have adequate power to reliably assess patient characteristics associated with a good or a poor response to either treatment. Although we used buprenorphine-naloxone tablets, we believe our results apply to all formulations of buprenorphine approved for the treatment of opioid dependence. Finally, buprenorphine and clinical care were provided to patients in both groups at no out-of-pocket costs. Some of our study design decisions could lead to our results overestimating the benefits of both treatments.

Conclusions

Our findings have implications for clinical care, patient education, research, and policy. Buprenorphine taper should be used sparingly, if at all, in primary care treatment of patients

dependent on prescription opioids. The poor treatment responses observed in our study and the potential consequences of relapse, including overdose and death, dictate that patients and providers should be aware of the likelihood of treatment failure and use caution when considering a taper. The low rate of naltrexone uptake further reinforces the limitations of a buprenorphine taper. Future research should be conducted that could help to identify factors that are associated with success with opioid agonist tapering and antagonist therapy initiation; that could help to identify clinical, genetic, or behavioral factors that may be harnessed and incorporated into algorithms for determining the likelihood of a good response to tapering or to maintenance therapy; or that could help to inform future treatment modalities. Despite the findings of the superiority of buprenorphine maintenance therapy compared with taper in our study, consistent with other studies of buprenorphine maintenance therapy, problems with persistent opioid use and retention with maintenance treatment support the need for research to improve outcomes and address concerns regarding diversion.[27,28,42–45] Policies that restrict access to, create financial burdens for, or place arbitrary limits on the duration of maintenance treatment should be reconsidered in the face of evidence that medication tapers lead to poorer outcomes.[46–50] The practice of of fice-based treatment with buprenorphine is now well established and has resulted in expanded treatment options and greater capacity of the treatment system,[51] which is of critical importance in the face of the rising epidemic of the non-medical use of prescription opioids and opioid dependence and the likely subsequent secondary surge in heroin and injection drug use, with attendant risks for infections and overdose.[52–54] Given the established efficacy of maintenance treatment with methadone and buprenorphine compared with medication tapering, expanded use of maintenance therapy and limited use of medication tapering and discontinuation should be the primary response to this chronic and relapsing medical condition.

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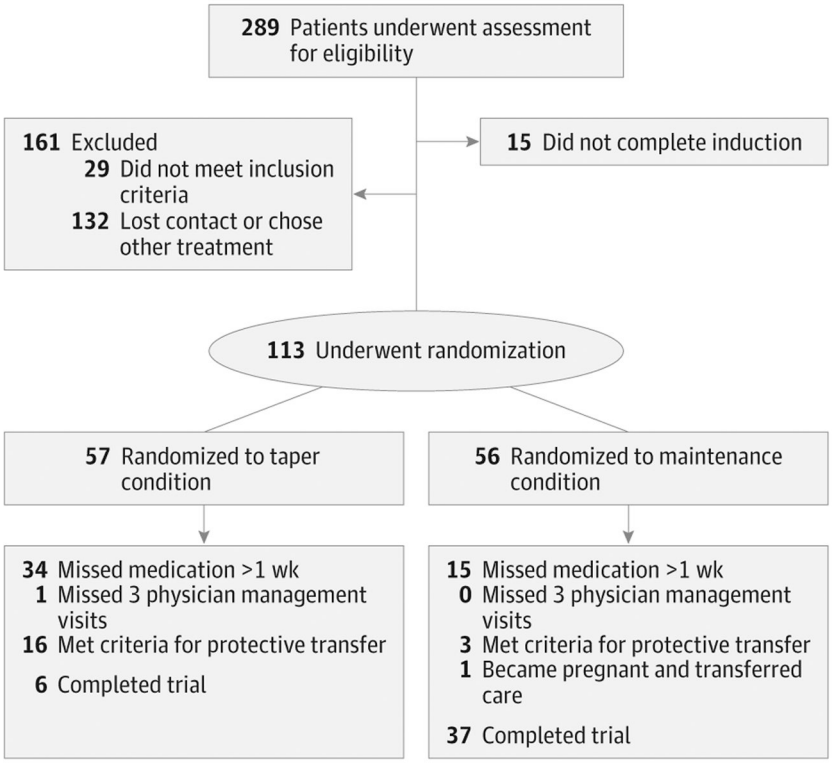
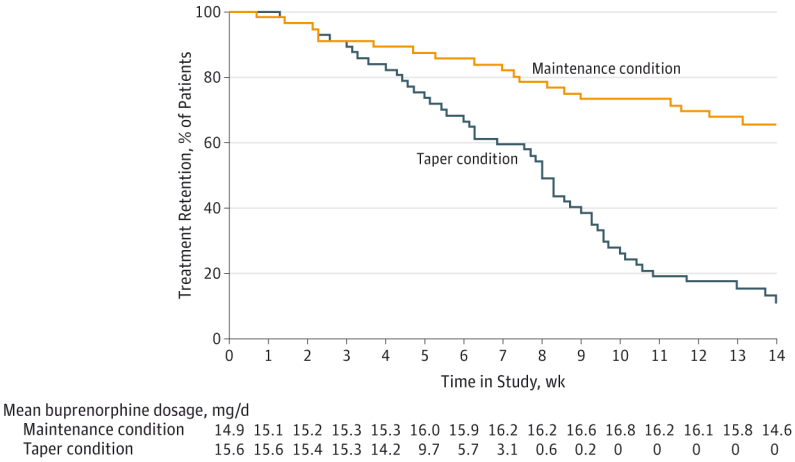


Figure 1.
CONSORT Flowchart of Enrollment, Treatment, and Follow-up



Mean buprenorphine dosage, mg/d														
Maintenance condition	14.9	15.1	15.2	15.3	15.3	16.0	15.9	16.2	16.2	16.6	16.8	16.2	16.1	15.8	14.6
Taper condition	15.6	15.6	15.4	15.3	14.2	9.7	5.7	3.1	0.6	0.2	0	0	0	0	0

Figure 2. Treatment Retention and Mean Buprenorphine Dosage for Patients With Prescription Opioid Dependence

Patients were assigned to the taper or the maintenance condition. Buprenorphine treatment was administered as a tablet formulation of buprenorphine hydrochloride and naloxone hydrochloride in a 4:1 ratio.

Table.

Baseline Demographic and Clinical Characteristics of Patients With Prescription Opioid Dependence Receiving Buprenorphine Treatment in Primary Care

Characteristic	Treatment Group[a]		*P* Value
	Taper (n = 57)	Maintenance (n = 56)	
Age, mean (95% CI), y	30.3 (28.0–32.6)	30.5 (27.9–33.1)	.88
Male sex	34 (60)	31 (55)	.64
White race	56 (98)	52 (93)	.16
Hispanic ethnicity	4 (7)	4 (7)	.68
Full-time employment[b]	23 (40)	25/53 (47)	.47
Educational level beyond high school[b]	36 (63)	35/53 (66)	.75
Never married[b]	37 (65)	34/53 (61)	.93
Duration of opioid dependence, mean (95% CI), y	4.5 (3.3–5.6)	4.9 (3.7–6.0)	.63
Provided an opioid-positive urine sample during induction and stabilization period	16 (28)	13 (23)	.55
Patient-reported illicit opioid use in the past 30 d, mean (95% CI), d	20.8 (18.9–22.7)	21.1 (19.2–23.0)	.88
Cocaine abuse	5 (9)	8 (14)	.36
Route of opioid administration, nasal or oral	56 (98)	56 (100)	.32
Prior therapy			
Attempted opioid detoxification	8 (14)	6 (11)	.54
Formal treatment for an opioid use disorder[c]	18 (33)	14 (25)	.37
Use of other substances in past 30 d, mean (95% CI), d			
Alcohol	2.4 (0.8–4.1)	5.6 (3.8–7.1)	.01
Cocaine	0.4 (0.2–1.0)	0.9 (0.3–1.5)	.23
Duration of induction and stabilization therapy, mean (95% CI), d	11.7 (10.9–12.4)	12.3 (11.6–13.1)	.24

[a]Buprenorphine treatment was administered as a tablet formulation of buprenorphine hydrochloride and naloxone hydrochloride in a 4:1 ratio. Unless otherwise indicated, data are expressed as number (percentage) of patients.

[b]Includes 53 patients in the maintenance group.

[c]Includes 55 patients in the taper group.