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Adjunctive Counseling During Brief and Extended Buprenorphine-Naloxone Treatment for Prescription Opioid Dependence

A 2-Phase Randomized Controlled Trial

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Context: No randomized trials have examined treatments for prescription opioid dependence, despite its increasing prevalence.

Objective: To evaluate the efficacy of brief and extended buprenorphine hydrochloride–naloxone hydrochloride treatment, with different counseling intensities, for patients dependent on prescription opioids.

Design: Multisite, randomized clinical trial using a 2-phase adaptive treatment research design. Brief treatment (phase 1) included 2-week buprenorphine-naloxone stabilization, 2-week taper, and 8-week postmedication follow-up. Patients with successful opioid use outcomes exited the study; unsuccessful patients entered phase 2: extended (12-week) buprenorphine-naloxone treatment, 4-week taper, and 8-week postmedication follow-up.

Setting: Ten US sites.

Patients: A total of 653 treatment-seeking outpatients dependent on prescription opioids.

Interventions: In both phases, patients were randomized to standard medical management (SMM) or SMM plus opioid dependence counseling; all received buprenorphine-naloxone.

Main Outcome Measures: Predefined "successful outcome" in each phase: composite measures indicating minimal or no opioid use based on urine test–confirmed self-reports.

Results: During phase 1, only 6.6% (43 of 653) of patients had successful outcomes, with no difference between SMM and SMM plus opioid dependence counseling. In contrast, 49.2% (177 of 360) attained successful outcomes in phase 2 during extended buprenorphine-naloxone treatment (week 12), with no difference between counseling conditions. Success rates 8 weeks after completing the buprenorphine-naloxone taper (phase 2, week 24) dropped to 8.6% (31 of 360), again with no counseling difference. In secondary analyses, successful phase 2 outcomes were more common while taking buprenorphine-naloxone than 8 weeks after taper (49.2% [177 of 360] vs 8.6% [31 of 360], $P<.001$). Chronic pain did not affect opioid use outcomes; a history of ever using heroin was associated with lower phase 2 success rates while taking buprenorphine-naloxone.

Conclusions: Prescription opioid–dependent patients are most likely to reduce opioid use during buprenorphine-naloxone treatment; if tapered off buprenorphine-naloxone, even after 12 weeks of treatment, the likelihood of an unsuccessful outcome is high, even in patients receiving counseling in addition to SMM.

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ABUSE OF PRESCRIPTION OPIOIDS is a significant public health and policy[1] concern, with increasing rates of nonmedical use,[2] emergency department visits,[3] addiction treatment episodes,[4] overdose deaths,[5] and costs[6] related to these drugs in recent years. Despite the growing prevalence of prescription opioid dependence and the availability and increasing use[7] of buprenorphine hydrochloride treatment (primarily as buprenorphine hydrochloride–naloxone hydrochloride) in physician offices, most opi-

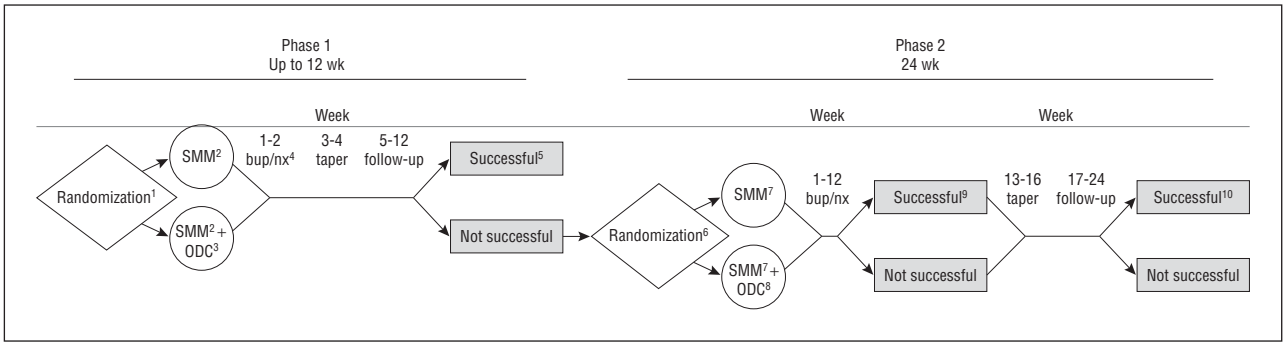

Figure 1. Study design. [1]Stratified by the presence or absence of a history of heroin use and current chronic pain. [2]Standard medical management (SMM); phase 1, week 1: 2 visits; weeks 2 to 4: 1 visit/wk; and weeks 5 to 8: biweekly visits. [3]Opioid dependence counseling (ODC); phase 1, weeks 1 to 4: 2 visits/wk; and weeks 5 to 8: biweekly visits. [4]Buprenorphine-naloxone (bup/nx) dose: 8 to 32 mg/d. [5]Phase 1 primary end point: completion of week 12 with self-reported opioid use on no more than 4 days in a month; absence of 2 consecutive opioid-positive urine test results, no additional substance use disorder treatment (other than self-help), and no more than 1 missing urine sample. [6]Stratified by phase 1 counseling condition, that is, SMM or SMM+ODC. [7]SMM; phase 2, week 1: 2 visits; and weeks 2 to 16: 1 visit/wk. [8]ODC; phase 2, weeks 1 to 6: 2 visits/wk; and weeks 7 to 12: 1 visit/wk. [9]Phase 2 primary end point: abstinent from opioid use during week 12 (the final week of bup/nx stabilization) and during at least 2 of the previous 3 weeks (weeks 9-11). [10]Phase 2 secondary end point: abstinent from opioid use during week 24 and during at least 2 of the previous 3 weeks (weeks 21-23).

oid dependence treatment research has been conducted with heroin-dependent patients receiving methadone in specialized opioid dependence treatment programs. It is notable, however, that in 2009, the use of a prescription opioid for nonmedical reasons was 20 times more common than was heroin use.[8] Moreover, almost 50% more people sought treatment for dependence on prescription opioids than for dependence on heroin.[8] Thus, studying treatments for individuals dependent on prescription opioids has clear public health importance.

Some research[9,10] has suggested that patients dependent on prescription opioids have more favorable prognostic characteristics than do those dependent on heroin, including shorter treatment histories, less injection use, fewer family and social problems, and less income from illegal sources. Indeed, a recent secondary analysis[9] found that patients dependent on prescription opioids (n=29) had less opioid use during office-based buprenorphine-naloxone treatment compared with those using heroin (n=124). Perhaps, then, patients dependent on prescription opioids respond to treatment differently than do those dependent on heroin.[11]

One area in which differential treatment response could manifest itself is in the role of counseling; the impact of counseling in the office-based treatment of individuals dependent on prescription opioids is unknown. Studies examining the role of counseling in the treatment of primarily heroin-dependent patients receiving methadone in specialized opioid treatment programs[12,13] have generally, although not always,[14] supported the role of drug counseling in improving outcomes, particularly abstinence from opioids.[12] In contrast, the largest study[15] of counseling in conjunction with buprenorphine-naloxone treatment in a primary care office–based setting found no difference between 2 levels of intensity of counseling, although the difference in intensity between the 2 counseling conditions (1 weekly session lasting either 20 or 45 minutes) was relatively small, and the sample was primarily (86%) heroin users.

Recent reviews of prescription opioid dependence[10,11] have also called for examination of the optimal length of pharmacotherapy in this population. Studies of heroin-dependent patients have favored maintenance treatment over detoxification[16]; no studies have examined this issue in patients dependent on prescription opioids.[10,11] In light of these patients' generally favorable prognostic characteristics and some evidence suggesting that they may achieve better outcomes than those dependent on heroin,[9] it has been suggested that fewer of these patients might require ongoing opioid agonist treatment.[10]

In summary, then, it is unclear whether findings from studies of heroin-dependent patients in methadone treatment programs are generalizable to those dependent on prescription opioids treated with buprenorphine in physician offices. We are aware of only 1 study[17] that has prospectively examined treatment outcomes in patients primarily using prescription opioids; this was a nonrandomized feasibility study with 15 patients, 7 of whom had also used heroin. We know of no published randomized controlled trials of treatments for patients dependent on prescription opioids. To help define optimal approaches for treating this rapidly growing population of prescription opioid–dependent patients, the National Institute on Drug Abuse Clinical Trials Network conducted the Prescription Opioid Addiction Treatment Study, a large-scale, multisite, prospective randomized controlled trial. We evaluated the efficacy of brief and extended buprenorphine-naloxone treatment, with different intensities of counseling, for 653 patients with prescription opioid dependence.

METHODS

STUDY DESIGN

The trial used a randomized, 2-phase, adaptive treatment research design[18] intended to approximate clinical practice (**Figure 1**). This type of study, which has been used in other types of medical research,[19] including psychiatry,[20] is designed to identify a treatment strategy for a disorder, including the optimal response to an initial treatment failure. As in the present study, more than 1 phase and more than 1 randomization process may be used to identify this strategy, a design known as a sequential multiple-assignment randomized trial.[18] In the present study, the response (successful or unsuccessful) to initial brief buprenorphine-naloxone treatment (phase

1) determined whether patients would require extended buprenorphine-naloxone treatment (phase 2); details of the study methods, including interventions, are described elsewhere.[21] Brief treatment (phase 1) consisted of buprenorphine-naloxone induction, 2 weeks of stabilization, a 2-week taper, and 8 weeks of follow-up. Patients who met the "successful outcome" criteria at week 12 (see the "End Points" subsection) exited the study. Unsuccessful patients were invited into phase 2 as soon as successful outcome was no longer attainable according to the protocol. Extended treatment (phase 2) consisted of 12 weeks of buprenorphine-naloxone stabilization, a 4-week taper, and 8 weeks of follow-up. In each phase, patients were randomized to (1) standard medical management alone (SMM)[22] or (2) SMM plus individual opioid dependence counseling (SMM+ODC).[23] Using a permuted block design, randomization was stratified in phase 1 by 2 potentially important prognostic variables[9,24]: (1) any history of heroin use and (2) chronic pain at baseline (see the "Assessments" subsection). In phase 2, patients were stratified by phase 1 treatment assignment: SMM or SMM+ODC. The institutional review boards at the study sites approved the study; participants gave written informed consent after the procedures were explained. Enrollment began June 12, 2006; the last visit occurred July 9, 2009.

STUDY POPULATION

Participants 18 years or older at 10 treatment sites met the *DSM-IV*[25] criteria for current dependence on prescription opioids. Other inclusion criteria were physiologic dependence and willingness to be detoxified from opioids, clearance from the prescribing physician if prescribed opioids for pain, provision of locator information, and birth control use for women of childbearing potential.

Potential study participants were excluded if they used heroin more than 4 days in the past month; had a lifetime opioid dependence diagnosis due to heroin alone[26]; had ever injected heroin[27]; required ongoing pain management with opioids; had experienced a major pain event in the past 6 months[27]; were prescribed methadone (>40 mg/d) for pain; were psychotic, suicidal, or otherwise psychiatrically unstable; participated in another medication study in the past month; were currently participating in formal substance abuse treatment (self-help groups, eg, Narcotics Anonymous, were allowed); were dependent on other substances and required immediate medical attention, for example, medical detoxification from alcohol; had liver function tests more than 5 times the upper limit of normal; or were pregnant or lactating.

TREATMENTS

Buprenorphine-Naloxone

Patients with a score greater than 8 on the Clinical Opiate Withdrawal Scale[28] were inducted onto sublingual buprenorphine-naloxone and were dispensed buprenorphine-naloxone for once-daily dosing at weekly SMM visits. Patients received 4 to 12 mg (in 4-mg doses) on the induction day, depending on their initial response to buprenorphine-naloxone. At each subsequent SMM visit, the study physician could adjust the buprenorphine-naloxone dose in increments of up to 8 mg/wk; the dose was adjusted for opioid use, withdrawal symptoms, adverse effects, and craving but not for pain. The allowable dose (expressed as buprenorphine) during stabilization was 8 to 32 mg/d, consistent with practice guidelines.[29] Nonopioid comfort medications (eg, loperamide for diarrhea) were permitted during medication tapers.

Standard Medical Management

Manual-based SMM, which has previously demonstrated efficacy,[30] was provided to all the participants by physicians certified to prescribe buprenorphine. During the initial session in each phase (45-60 minutes in phase 1 and 30-60 minutes in phase 2), the physician reviewed the patient's medical, psychiatric, and substance use problems; recommended abstinence; and referred the patient to self-help groups. In subsequent 15- to 20-minute visits, the physician assessed substance use, craving, and buprenorphine-naloxone response; recommended abstinence and self-help participation; and prescribed buprenorphine-naloxone (see Figure 1 for the visit schedule).

Opioid Dependence Counseling

In addition to SMM, half the patients were randomly assigned to receive manual-based ODC,[23] delivered in 45- to 60-minute sessions by trained substance abuse or mental health professionals (Figure 1). The ODC was based on drug counseling manuals[31,32] with demonstrated efficacy,[33,34] modified for this study of prescription opioid dependence treatment with buprenorphine. Counselors educated patients about addiction and recovery, recommended self-help groups, and emphasized lifestyle change. Using a skills-based format with interactive exercises and take-home assignments, ODC covered a wider range of relapse prevention issues in greater depth than did SMM, including coping with high-risk situations, managing emotions, and dealing with relationships.

ASSESSMENTS

The Composite International Diagnostic Interview[35] was administered at baseline to diagnose opioid dependence, other substance-related disorders, major depressive disorder, and posttraumatic stress disorder. Urine samples for drugs of abuse (including the opioid analgesics oxycodone, hydrocodone, hydromorphone, morphine, codeine, propoxyphene, and methadone) and self-reports of substance use were collected weekly during treatment and biweekly during follow-up; a calendar-based interview technique[36] reviewed each day since the previous visit. Opioid withdrawal was assessed at each SMM visit using the 11-item Clinical Opiate Withdrawal Scale.[28] Pain intensity and pain-related interference with life functioning were assessed via self-report at baseline and monthly using the Brief Pain Inventory–Short Form.[37] Patients were designated at baseline as having current chronic pain if they reported pain "other than everyday kinds of pain,"[37] excluding withdrawal-related pain, for at least 3 months.[38]

END POINTS

For both study phases, we specified dichotomous successful outcomes as a priori primary end points in each phase. In both phases, the definition of "successful outcome" was based on specifying a clinically meaningful end point that would guide a treating physician in deciding whether to continue with the current treatment strategy or change course. In phase 1, successful outcome was, thus, defined as completing week 12 with self-reported opioid use on no more than 4 days in a month, absence of 2 consecutive opioid-positive urine test results, no additional substance use disorder treatment (other than self-help), and no more than 1 missing urine sample during the 12 weeks. Consistent with the adaptive treatment research design,[18] patients who were unsuccessful in phase 1, for example, by reporting more than 4 days of opioid use in a month, became immediately eligible for phase 2 even if they

had not completed phase 1. In phase 2, successful outcome was defined as abstaining from opioids during week 12 (the final week of buprenorphine-naloxone stabilization) and during at least 2 of the previous 3 weeks (weeks 9-11); this outcome measure, which required substantial improvement but not complete abstinence, is similar to that used to represent a "good clinical outcome" in the COMBINE (Combined Pharmacotherapies and Behavioral Interventions) Study, a multisite study examining optimal combinations of medications and behavioral therapies for alcohol dependence.[39] The definition of successful outcome in the 2 phases differed slightly because the study was designed to facilitate rapid transition from phase 1 to phase 2 for patients returning to opioid use; hence, unlike in phase 2, unsuccessful patients ended phase 1 at different times, by design. Abstinence was determined by urine test–verified self-reports; missing urine samples were considered positive for opioids.[40] A planned secondary outcome, successful outcome at week 24, that is, 8 weeks after completion of the phase 2 buprenorphine-naloxone taper, was defined the same as at week 12 of phase 2, that is, abstinent from opioids during week 24 and at least 2 of the previous 3 weeks.

STATISTICAL ANALYSIS

The primary analysis compared the 2 treatment conditions (SMM vs SMM+ODC) with respect to the phase 2 primary end point using a 2-sided significance level $\alpha = .05$. Based on a test statistic proposed by Liu and Liang[41] using generalized estimating equations to account for correlation among measurements of patients from the same site, we determined that 324 participants would be needed for phase 2 to ensure sufficient power (≥80%) of a 2-sided significance test with $\alpha = .05$ to detect a 15% or greater difference in successful outcomes between the 2 treatment conditions. To achieve this sample size, we estimated that approximately twice that number of participants (ie, 648) would be needed in phase 1. This figure was based on estimates that 20% of phase 1 patients would achieve successful outcomes and that 40% of those with unsuccessful outcomes in phase 1 (30% of all randomized patients) would be ineligible, would be unreachable, or would refuse to participate in phase 2.

The analyses comparing counseling conditions were based on the intention-to-treat population, which includes all randomized patients; patients were compared according to the group to which they were assigned at randomization, regardless of their treatment attendance. According to end point definitions, missing urine samples were considered positive for opioid use. Between-treatment comparisons used generalized estimating equation models to account for the correlation among outcomes of participants from the same site. Model-based statistics were considered for inference. Phase 1 models included as covariates the phase 1 randomization stratification factors, that is, chronic pain at baseline and history of heroin use. Phase 2 models also included treatment assignment from phase 1. Interactions between the randomized treatment and randomization stratification factors (baseline heroin use and chronic pain status) as well as site were considered.

In addition to the primary analysis, we prespecified the main secondary analyses to help avoid overinterpretation; this consisted of examining the effect of the 2 phase 1 stratification variables (ie, chronic pain at baseline and history of heroin use) on the primary end points. The actual *P* value for each comparison is reported to aid in interpretation of the overall conclusions. A generalized linear mixed model was used to compare treatment success between different time points. Analyses were conducted using PROC GENMOD and PROC GLIMMIX in SAS (SAS Institute Inc, Chicago, Illinois).

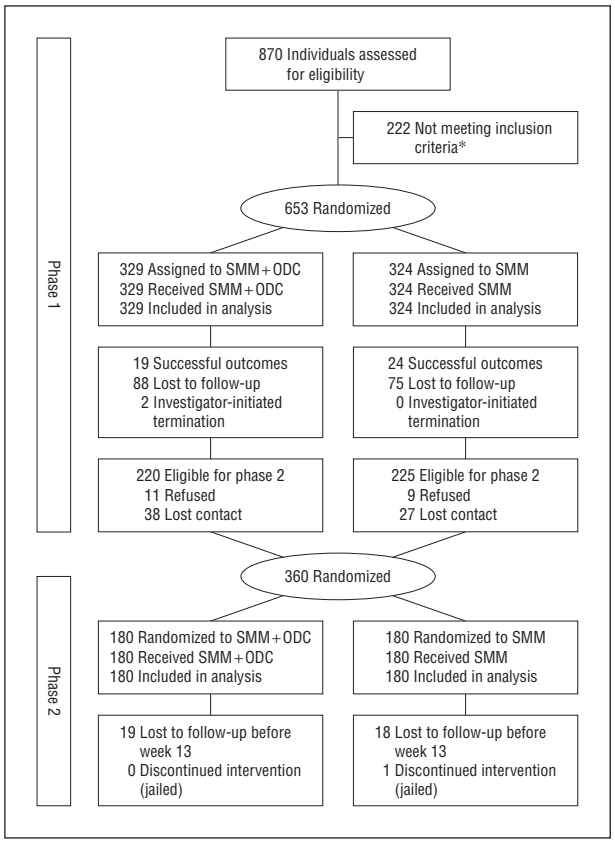

Figure 2. Randomization, treatment, and follow-up of the study patients. *Reasons (n=315) for not meeting the inclusion or exclusion criteria were as follows: not physically dependent on opioids (n=47); unable to meet the study requirements (n=39); psychotic or psychiatrically unstable (n=34); not in good general health (n=32); did not meet the *DSM-IV* criteria for current opioid dependence (n=32); medical condition made participation medically hazardous (n=25); no medical clearance from the treating physician prescribing opioids (n=23); traumatic or major pain event (n=18); heroin use more than 4 days in the past 30 days (n=18); history of opioid use as a result of heroin use (n=17); dependent on alcohol, sedative-hypnotics, or stimulants (n=10); required ongoing pain management (n=10); participated in methadone treatment/methadone dose greater than 40 mg (n=4); pending surgery (n=3); and liver function test results 5 times the upper limit of normal (n=3). A participant could be represented in more than 1 category of the reasons for noneligibility; 5 patients who did not meet all the inclusion criteria were randomized. ODC indicates opioid dependence counseling; and SMM, standard medical management.

RESULTS

STUDY ENROLLMENT AND SAMPLE CHARACTERISTICS

The sociodemographic and clinical characteristics of the patients enrolled (**Figure 2**) did not differ between treatment groups (**Table 1**).

SESSION ATTENDANCE, MEDICATION DOSE, AND PROTOCOL ADHERENCE

In phase 1, patients attended a mean (SD) of 4.5 (1.5) SMM visits (81.5% of the maximum possible number of visits) and 6.6 (3.5) ODC sessions (71.7% of the maximum possible); during phase 2, patients attended a mean (SD) of 14.0 (4.2) SMM visits (82.4% of the maximum),

Table 1. Background and Clinical Characteristics by Counseling Condition at Baseline

Patient Characteristics	SMM+ODC (n=329)	SMM (n=324)	Total (N=653)	*P* Value
Sociodemographics				
Female sex, No. (%)	125 (38.0)	136 (42.0)	**261** (40.0)	.30
Age, mean (SD), y	32.9 (10.1)	33.5 (10.3)	33.2 (10.2)	.46
White race, No. (%)	301 (91.5)	295 (91.0)	**596** (91.3)	.94
Education, mean (SD), y	13.0 (2.0)	13.0 (2.3)	13.0 (2.2)	.86
Never married, No. (%)[a]	162 (49.2)	164 (50.6)	**326** (49.9)	.72
Employed full-time, No. (%)	210 (63.8)	201 (62.0)	**411** (62.9)	.64
Clinical				
Substance use				
Nonopioid substance dependence diagnoses, No. (%)				
Alcohol				
Past year	14 (4.3)	11 (3.4)	**25** (3.8)	.57
Lifetime	80 (24.3)	93 (28.7)	**173** (26.5)	.20
Cannabis				
Past year	15 (4.6)	19 (5.9)	**34** (5.2)	.45
Lifetime	49 (14.9)	52 (16.0)	**101** (15.5)	.68
Cocaine				
Past year	11 (3.3)	11 (3.4)	**22** (3.4)	.97
Lifetime	59 (17.9)	59 (18.2)	**118** (18.1)	.93
Other stimulants				
Past year	6 (1.8)	7 (2.2)	**13** (2.0)	.76
Lifetime	31 (9.4)	40 (12.3)	**71** (10.9)	.23
Sedatives				
Past year	17 (5.2)	23 (7.1)	**40** (6.1)	.30
Lifetime	30 (9.1)	35 (10.8)	**65** (10.0)	.47
None				
Past year	282 (85.7)	268 (82.7)	**550** (84.2)	.29
Lifetime	180 (54.7)	164 (50.6)	**344** (52.7)	.30
Days of substance use in the past 30 d, mean (SD)				
Opioid analgesics[b]	27.9 (4.3)	28.2 (3.6)	28.1 (4.0)	.33
Cannabis	5.2 (9.7)	4.5 (9.1)	4.9 (9.4)	.39
Sedative-hypnotics, nonbarbiturate	3.8 (7.8)	2.7 (8.0)	3.8 (7.9)	.87
Alcohol	3.3 (6.2)	2.6 (5.8)	3.0 (6.0)	.18
Amphetamines	0.7 (3.9)	0.4 (2.6)	0.5 (3.3)	.20
Cocaine	0.5 (1.7)	0.5 (2.3)	0.5 (2.0)	.80
Barbiturates	0.1 (1.2)	0.3 (2.6)	0.2 (2.0)	.19
Heroin	0.2 (0.7)	0.1 (0.4)	0.1 (0.6)	.07
>1 Drug	10.6 (11.2)	10.4 (11.4)	10.5 (11.3)	.83
Ever used heroin, No. (%)	74 (22.5)	76 (23.5)	**150** (23.0)	.77
Years of opioid use, mean (SD)	4.8 (4.3)	5.5 (5.1)	5.2 (4.7)	.08
Previous opioid use disorder treatment, No. (%)	99 (30.1)	111 (34.3)	**210** (32.2)	.25
Pain				
Current chronic pain, No. (%)	139 (42.2)	135 (41.7)	**274** (42.0)	.88
Severity, mean (SD)[c]	4.4 (2.2)	4.4 (2.1)	4.4 (2.2)	.95
Interference with general activities, mean (SD)[c]	4.2 (2.6)	4.2 (2.7)	4.2 (2.7)	.85

Abbreviations: ODC, opioid dependence counseling; SMM, standard medical management.
[a] Based on 238 participants in the SMM+ODC group and 323 in the SMM group (N = 651).
[b] The most commonly used opiate analgesics in the past 30 days were oxycodone, extended-release, 35.2%; hydrocodone, 32.3%; oxycodone, immediate-release, 18.7%; methadone, 6.4%; morphine, 2.1%; and other, 5.3%.
[c] Brief Pain Inventory scores (range, 0-10) are based on 274 participants with chronic pain.

and 11.6 (5.2) ODC sessions (64.4% of the maximum). Based on Wilcoxon rank sum tests, mean (SD) attendance at SMM visits did not vary by counseling condition in either phase (SMM+ODC vs SMM: 4.4 [1.5] vs 4.5 [1.5], $z=1.24$, $P=.39$ during phase 1 and 14.1 [4.4] vs 13.9 [4.0], $z=0.86$, $P=.21$ during phase 2).

The most frequently prescribed maximum dose of buprenorphine in phase 1 was 16 mg (n=249 of 653 patients, 38.1%), followed by 12 mg (n=116, 17.8%), 24 mg (n=86, 13.2%), 20 mg (n=62, 9.5%), 8 mg (n=53, 8.1%), and other doses (n=87, 13.3%). In phase 2, 16 mg (n=99 of 360 patients, 27.5%) and 24 mg (n=57, 15.8%) were the most frequently prescribed maximum doses, followed by 12 mg (n=51, 14.2%), 20 mg (n=50, 13.9%), 32 mg (n=39, 10.8%), and other doses (n=64, 17.8%). Medication adherence was measured by self-report, which was aided by pill count. Adherence was high: 95.5% and 98.1% of doses were reported to be taken as prescribed during phases 1 and 2, respectively.

All SMM and ODC sessions were audiotaped and evaluated by independent raters to monitor clinician adherence to treatment manuals; 98.9% of sessions received acceptable ratings, and 4 of 91 clinicians required additional training.

Table 2. Successful Opioid Use Outcome by Counseling Condition (SMM vs SMM+ODC) at 3 Time Points

Time Point	Observed, No./Total No. (%) [95% CI]		GEE Model–Based Results	
	SMM	SMM+ODC	OR (95% CI)[a]	*P* Value
End of phase 1	24/324 (7.4) [4.8-10.8]	19/329 (5.8) [3.5-8.9]	1.3 (0.7-2.4)[b]	.36
Phase 2, end of treatment	84/180 (46.7) [39.2-54.2]	93/180 (51.7) [44.1-59.2]	0.8 (0.5-1.2)[c]	.27
Phase 2, 8-wk posttreatment follow-up	13/180 (7.2) [3.9-12.0]	18/180 (10.0) [6.0-15.3]	0.7 (0.3-1.3)[c]	.22

Abbreviations: GEE, generalized estimating equation; ODC, opioid dependence counseling; OR, odds ratio; SMM, standard medical management.
[a] The reference category is SMM+ODC.
[b] Adjusted for chronic pain at baseline and lifetime history of heroin use.
[c] Adjusted for chronic pain at baseline, lifetime history of heroin use, and phase 1 randomization.

Table 3. Successful Opioid Use Outcome by the Phase 2 Time Point GLMM-Based Results

Phase 2 Time Point	Observed, No./Total No. (%) [95% CI]	OR (95% CI)	*P* Value
End of treatment	177/360 (49.2) [43.9-54.5]	10.6 (7.2-15.6)[a]	<.001
8-wk posttreatment follow-up	31/360 (8.6) [5.9-12.0]		

Abbreviations: GLMM, generalized linear mixed model; OR, odds ratio.
[a] The reference category is 8-wk posttreatment follow-up.

OPIOID USE OUTCOMES

Overall, 43 of 653 patients (6.6%) had successful outcomes with brief buprenorphine-naloxone treatment in phase 1, with no difference in success rates between those receiving SMM alone and those receiving SMM+ODC (**Table 2**). In contrast, 49.2% of patients (177 of 360) attained successful outcomes in extended treatment (phase 2) while still taking buprenorphine-naloxone (week 12). As in phase 1, there was no difference between counseling conditions. Overall success rates 8 weeks after completing the buprenorphine-naloxone taper in phase 2 (week 24) dropped to 8.6% (31 of 360 patients), again with no difference between counseling conditions. Results of comparisons between counseling conditions did not vary by sex or race; there was no site × treatment interaction. During phase 2, patients were considerably more likely to attain success while continuing treatment with buprenorphine-naloxone (week 12) than 8 weeks after completing the buprenorphine-naloxone taper (week 24), controlling for counseling condition (49.2% vs 8.6%, $P<.001$) (**Table 3**). Similar results were found when we defined success as complete abstinence from opioid use in the previous 4 weeks. Seventy of the 180 patients (38.9%) receiving SMM+ODC abstained completely from opioid use during weeks 9 to 12 of phase 2 (ie, while still taking buprenorphine-naloxone), whereas 61 of 180 SMM patients (33.9%) achieved that outcome ($P=.25$). At week 24, 8 weeks after completing the buprenorphine-naloxone taper, only 13 of 180 SMM+ODC patients (7.2%) had been abstinent from opioid use during the previous 4 weeks compared with 11 of 180 SMM patients (6.1%; $P=.59$). The rate of complete abstinence from opioid use was significantly higher at week 12 than at week 24 (36.4% vs 6.7%, $P<.001$).

Urine test results corroborated these results: the rate of opioid-positive urine test results in phase 2 was significantly higher during the combined taper and posttaper periods (weeks 13-24) than while maintained on buprenorphine-naloxone during weeks 1 to 12 (58.1% vs 39.1%, $P<.001$).

IMPACT OF CHRONIC PAIN AND LIFETIME HEROIN USE ON OPIOID USE OUTCOMES

As a planned secondary analysis, we examined the impact of the 2 phase 1 stratification variables on the primary end points. Chronic pain at baseline was not related to outcomes either in phase 1 or during phase 2 while taking buprenorphine-naloxone; 30 of 379 patients (7.9%) with chronic pain achieved success in phase 1 compared with 13 of 274 (4.7%) without chronic pain ($P=.25$). Seventy-nine of 149 phase 2 patients (53.0%) with chronic pain achieved success at week 12 compared with 98 of 211 patients (46.4%) without chronic pain ($P=.25$).

In contrast, patients with any lifetime use of heroin (n=100) were less likely than non–heroin users (n=260) to have successful phase 2 outcomes while receiving buprenorphine-naloxone (37.0% vs 53.8%, $P=.002$). A history of any heroin use did not affect phase 1 outcomes (6.0% [9 of 150] vs 6.8% [34 of 503] success rates for those with and without heroin use histories, respectively). There was no interaction between either of these 2 factors and study treatment.

ADVERSE EVENTS

In phase 1, most patients (n=542, 83.0%) experienced 1 or more adverse events, most commonly headache (n=191, 29.2%), constipation (n=104, 15.9%), and insomnia (n=86, 13.2%); few patients (n=15, 2.3%) discontinued treatment as a result of an adverse event. In phase 2, most patients (n=216, 60.0%) experienced 1 or more adverse events, most commonly headache (n=98, 27.2%), nasopharyngitis (n=86, 23.9%), and nausea (n=61, 16.9%), resulting in 9 patients (2.5%) discontinuing treatment. There were 12 serious adverse events

in phase 1 and 24 in phase 2 (in 21 patients). Psychiatric symptoms were the most common serious adverse events (7 of 36), particularly depression leading to hospitalization (n=5); all of these occurred soon after completion of the phase 1 (n=2) or phase 2 (n=3) taper.

COMMENT

In this multisite study, the first large randomized controlled trial of patients dependent on prescription opioids, the rate of unsuccessful outcomes after buprenorphine-naloxone taper, even after a 12-week treatment, was high, exceeding 90%. In contrast, patients stabilized with buprenorphine-naloxone treatment had considerably better opioid use outcomes than did those who had been tapered off the medication. The addition of individual ODC to buprenorphine-naloxone treatment plus medical management did not improve opioid use outcomes. The high rate of unsuccessful outcomes after buprenorphine-naloxone taper is notable in light of the good prognostic characteristics[42] of the population (ie, largely employed, well educated, relatively brief opioid use histories, and little other current substance use) and previous research suggesting that patients dependent on prescription opioids might have better outcomes than those dependent on heroin.[9] The number of psychiatric serious adverse events in the posttaper period was low, similar to that in other studies of opioid-dependent patients[40]; nevertheless, physicians should monitor psychiatric symptoms when tapering these patients from opioids.

The present findings suggest that physicians can successfully treat many patients dependent on prescription opioids, with or without chronic pain, using buprenorphine-naloxone with relatively brief weekly medical management visits; half of the sample did well during this 12-week regimen. Consistent with results from a previous study[15] of predominantly heroin-dependent patients receiving buprenorphine-naloxone in a primary care setting, individual drug counseling did not improve opioid use outcomes when added to weekly medical management visits. Similar to that study, we did not include a condition providing infrequent or no medical management. It is unknown whether providing less intensive medical management, perhaps in conjunction with group counseling, would affect outcomes, which is of particular interest because not all physicians who treat opioid dependence with buprenorphine see patients as often as weekly.[7] Conversely, more frequent ODC, such as that provided in an intensive outpatient treatment program, might have produced better outcomes than did SMM+ODC. Moreover, alternative models of behavioral intervention, for example, contingency management,[43] might improve outcomes in this population given that approximately half of those receiving buprenorphine-naloxone stabilization did not achieve successful outcomes.

The length of this trial may have affected the results as well. Studies[44,45] of methadone maintenance treatment with heroin-dependent patients have shown that patients who participate in longer-term treatment (eg, a year or more) have better outcomes. It is not known, however, whether SMM+ODC would have outperformed SMM if delivered for a longer period. Moreover, it is unclear whether a taper after longer treatment with buprenorphine-naloxone would yield a better outcome.

The finding regarding the substantial drop in the rate of successful outcomes in phase 2 that occurred after the buprenorphine-naloxone taper must be interpreted with some caution because the study design did not include a control group of patients who were not tapered. However, this concern is mitigated by the aforementioned evidence from the literature regarding treatment of opioid dependence, which has consistently demonstrated the benefit of longer-term opioid agonist treatment.[44,45]

The presence of chronic pain did not affect opioid use outcomes. Chronic pain is highly prevalent in patients dependent on prescription opioids[46-48] and was present in nearly half of the present study population, albeit of relatively moderate intensity overall. Indeed, if treating physicians deemed their patients' pain to be severe enough to require ongoing opioid therapy, they were excluded from the study. It is not known whether these findings can be generalized to patients with severe pain or patients seeking treatment for pain rather than for opioid dependence. Previous research had shown that individuals with co-occurring pain and substance dependence seem to respond poorly to addiction treatment[24] except in the context of opioid maintenance therapy.[49] This was the first study, however, to examine this topic prospectively in a population comprised exclusively of those dependent on prescription opioids. The negative prognostic impact of even minimal lifetime heroin use on outcome while maintained on buprenorphine-naloxone was notable, especially because we excluded individuals with substantial heroin use histories, including any heroin injection. It is unclear whether this was attributable to heroin use itself, population differences, or some other factor.

The strengths of this study include the large, national multisite study sample and the broad inclusion criteria, including patients with and without chronic pain. Consistent with other opioid dependence treatment studies,[15,40] the present study was limited by the high dropout rate from phase 1 to phase 2, although the dropout rate did not vary by treatment condition.

This study has important implications for clinical practice. The lack of a difference between SMM and SMM+ODC was similar to the finding of Fiellin et al[15] with a largely heroin-dependent population, despite the fact that we had a greater contrast in intensity of counseling conditions than did that study. This supports the national trend toward treatment of opioid dependence by physicians in office-based practice.[7] Furthermore, patients dependent on prescription opioids, with or without chronic pain, are most likely to reduce their opioid use during the first several months of treatment while receiving buprenorphine-naloxone; if tapered off this medication, the likelihood of relapse to opioid use or dropout from treatment is overwhelmingly high. The present findings raise an important question: What length of buprenorphine-naloxone treatment, if any, would lead to substantially better outcomes after a taper? This is a topic of clinical and research interest.

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