Adjunctive Counseling During Brief and Extended Buprenorphine-Naloxone Treatment for Prescription Opioid Dependence: A 2-Phase Randomized Controlled Trial

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Abstract

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-naloxone treatment, with different counseling intensities, for patients dependent upon prescription opioids.


Design—Multi-site, randomized clinical trial, using a two-phase adaptive treatment research design. Brief treatment (Phase 1) included 2-week buprenorphine-naloxone stabilization, 2-week taper, and 8-week post-medication 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 post-medication follow-up.

Main outcome measures—Pre-defined “successful outcome” in each phase: composite measures indicating minimal or no opioid use, based on urine-confirmed self-reports.

Interventions—In both phases, patients were randomized to Standard Medical Management (SMM) or SMM+Opioid Drug Counseling (ODC); all received buprenorphine-naloxone.

Results—During Phase 1, only 6.6% (43/653) of patients had successful outcomes, with no difference between the SMM and SMM+ODC. In contrast, 49.2% (177/360) 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 sharply to 8.6% (31/360), again with no counseling difference. In secondary analyses, successful Phase 2 outcomes were far more
common while taking buprenorphine-naloxone than 8 weeks post-taper (49.2% (177/360) vs. 8.6% (31/360), p<0.001). 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 unsuccessful outcome is extremely high, even among patients receiving counseling in addition to medical management.

**Trial Registration**—ClinicalTrials.gov number NCT00316277

Abuse of prescription opioids is a significant public health and policy concern, with increasing rates of non-medical use, emergency department visits, addiction treatment episodes, overdose deaths, and costs related to these drugs in recent years. Despite the growing prevalence of prescription opioid dependence and the availability and increasing utilization of buprenorphine treatment (primarily as buprenorphine-naloxone) in physician offices, most opioid 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, use of a prescription opioid for non-medical reasons was 20 times more common than heroin use. Moreover, nearly 50% more people sought treatment for dependence upon prescription opioids than for dependence upon heroin. Thus, studying treatments for individuals dependent upon prescription opioids has clear public health importance.

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

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 those dependent upon 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 have generally, although not always, supported the role of drug counseling in improving outcomes, particularly abstinence from opioids. In contrast, the largest study of counseling in conjunction with buprenorphine-naloxone in a primary care office-based setting found no difference between two levels of intensity of counseling, although the difference in intensity between the two counseling conditions (one 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 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; no studies have examined this issue in patients dependent upon prescription opioids. In light of these patients’ generally favorable prognostic characteristics and some evidence suggesting that they may achieve better outcomes than those dependent upon heroin, it has been suggested that fewer of these patients might require ongoing opioid agonist treatment.
In summary, then, it is unclear whether findings from studies of heroin-dependent patients in methadone treatment programs are generalizable to those dependent upon prescription opioids who are treated with buprenorphine in physician offices. We are aware of only one study\textsuperscript{17} that has prospectively examined treatment outcomes in patients primarily using prescription opioids; this was a non-randomized 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 upon 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 (POATS), a large-scale multi-site prospective randomized controlled trial. We evaluated the efficacy of brief and extended buprenorphine-naloxone treatment, with different intensities of counseling, or 653 patients with prescription opioid dependence.

Methods

Study design

The trial employed a randomized, two-phase adaptive treatment research design\textsuperscript{18} (Figure 1), intended to approximate clinical practice. This type of study, which has been used in other types of medical research,\textsuperscript{19} including psychiatry,\textsuperscript{20} is designed to identify a treatment strategy for a disorder, including the optimal response to an initial treatment failure. As in our study, more than one phase and more than one randomization process may be used to identify this strategy, a design known as a sequential multiple assignment randomized trial.\textsuperscript{18} In our 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 study methods, including interventions, are described elsewhere.\textsuperscript{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 “successful outcome” criteria at week 12 (see “Endpoints”) 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 an 8-week follow-up. In each phase, patients were randomized to 1) Standard Medical Management alone (SMM\textsuperscript{22}) or 2) SMM plus individual Opioid Dependence Counseling (SMM+ODC\textsuperscript{23}). Using a permuted-block design, randomization was stratified in Phase 1 by two potentially important prognostic variables: 9, 24 1) any history of heroin use, and 2) chronic pain at baseline (see “Assessments”). In Phase 2, patients were stratified by Phase 1 treatment assignment: SMM or SMM+ODC. The Institutional Review Boards at study sites approved the study; participants gave written informed consent after procedures were explained. Enrollment began June 12, 2006; the last visit occurred on July 9, 2009.

Study population

Participants age 18 or older at ten treatment sites met DSM-IV\textsuperscript{25} criteria for current dependence on prescription opioids. Other inclusion criteria were physiological 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 subjects were excluded if they used heroin >4 days in the past month; had a lifetime opioid dependence diagnosis due to heroin alone;\textsuperscript{26} had ever injected heroin;\textsuperscript{27} required ongoing pain management with opioids; had experienced a major pain event within the past 6 months;\textsuperscript{27} were prescribed methadone >40 mg a day 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, e.g., Narcotics Anonymous, were allowed); were dependent on other substances and required immediate medical attention, e.g., medical detoxification from alcohol; had liver function tests >5 times the upper limit of normal; or were pregnant or lactating.

**Treatments**

**Buprenorphine-Naloxone**—Patients with a score of >8 on the Clinical Opioid Withdrawal Scale\(^28\) were inducted onto sublingual buprenorphine-naloxone and were dispensed buprenorphine-naloxone for once-daily dosing at weekly SMM visits. Patients received 4–12 mg (in 4 mg doses) on the induction day, depending upon 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 per week; dose was adjusted for opioid use, withdrawal symptoms, side effects, and craving, but not pain. The allowable dose (expressed as buprenorphine) during stabilization was 8–32 mg per day, consistent with practice guidelines.\(^29\) Non-opioid comfort medications (e.g., loperamide for diarrhea) were permitted during medication tapers.

**Standard Medical Management (SMM)**—Manual-based SMM, which has previously demonstrated efficacy,\(^30\) was delivered to all participants by physicians certified to prescribe buprenorphine. During the initial session in each phase (45–60 minutes in Phase 1, 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 15–20 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 visit schedule).

**Opioid Dependence Counseling (ODC)**—In addition to SMM, half the patients were randomly assigned to receive manual-based ODC,\(^23\) delivered in 45–60 minute sessions by trained substance abuse or mental health professionals (Figure 1). 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 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 bi-weekly during follow-up; a calendar-based interview technique\(^36\) reviewed each day since the prior visit. Opioid withdrawal was assessed at each SMM visit with 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 ≥3 months.\(^38\)
Endpoints

For both study phases, we specified dichotomous “successful” outcomes as a priori primary endpoints in each phase. In both phases, our definition of “successful outcome” was based on specifying a clinically meaningful endpoint that would guide a treating clinician 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 ≤4 days in a month, absence of 2 consecutive opioid-positive urine tests, no additional substance use disorder treatment (other than self-help), and ≤1 missing urine sample during the 12-week period. Consistent with the adaptive treatment research design, patients who were “unsuccessful” in Phase 1, e.g., by reporting >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 ≥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 study, a multi-site study examining optimal combinations of medications and behavioral therapies for alcohol dependence. The definition of successful outcome in the two 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-verified self-reports; missing urines were considered positive for opioids. A planned secondary outcome, successful outcome at week 24, i.e., 8 weeks following completion of the Phase 2 buprenorphine-naloxone taper, was defined the same as at week 12 of Phase 2, i.e., abstinent from opioids during week 24 and ≥2 of the previous 3 weeks.

Statistical analysis

The primary analysis compared the two treatment conditions (SMM versus SMM+ODC) with respect to the Phase 2 primary endpoint, using a two-sided significance level α=0.05. Based on a test statistic proposed by Liu and Liang, employing generalized estimating equations to account for correlation among measurements of patients from the same site, we determined that a total of 324 subjects would be needed for Phase 2 to ensure sufficient power (≥80%) of a two-sided significance test with α=0.05 to detect a ≥15% difference in successful outcomes between the two treatment conditions. To achieve this sample size, we estimated that approximately twice that number of subjects (i.e., 648) would be needed in Phase 1. This figure was based on our 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 either be ineligible, be unreachable, or would refuse to participate in Phase 2.

The analyses comparing counseling conditions were based on the intent-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 endpoint definitions, missing urine samples were considered positive for opioid use. Between-treatment comparisons used generalized estimating equations 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, i.e., 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 pre-specified the main secondary analyses to help avoid over-interpretation; this consisted of examining the effect of the two Phase 1 stratification variables (i.e., chronic pain at baseline and history of heroin use) on the primary endpoints. The actual p-value for each comparison is reported to aid in the interpretation of the overall conclusions. A generalized linear mixed model compared treatment success between different time points. Analyses were conducted using PROC GENMOD and PROC GLIMMIX in SAS (2003).

Results

Study enrollment and sample characteristics

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 of 4.5 (standard deviation=1.5) SMM visits (81.5% of the maximum possible number of visits) and 6.6 (sd=3.5) ODC sessions (71.7% of maximum possible); during Phase 2, patients attended a mean of 14.0 (sd=4.2) SMM visits (82.4% of maximum), and 11.6 (sd=5.2) ODC sessions (64.4% of maximum). Based on Wilcoxon rank sum tests, attendance at SMM visits did not vary by counseling condition in either phase (4.4, sd=1.5 vs 4.5, sd=1.5; z=1.24, p=.39 during Phase 1; and 14.1, sd=4.4 vs 13.9, sd=4.0; z=.86, p=.21 during Phase 2; for SMM+ODC vs. SMM respectively).

The most frequently prescribed maximum dose of buprenorphine in Phase 1 was 16 mg (n=249, 38.3% of 653 patients), 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, 27.5% of 360 patients) 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 audiorecorded 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.

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 SMM+ODC (Table 2). In contrast, 49.2% (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 sharply to 8.6% (31 of 360), again with no difference between counseling conditions. Results of comparisons between counseling conditions did not vary by sex or race; there was no site-by-treatment interaction. During Phase 2, patients were considerably more likely to attain success while maintained on buprenorphine-naloxone (week 12) than 8 weeks after completing the buprenorphine-naloxone taper (week 24), controlling for counseling condition (49.2% versus 8.6%, p<0.001; Table 3). Similar results were found when we defined “success” as complete abstinence from opioids in the previous 4 weeks. Seventy of the 180 patients receiving SMM+ODC (38.9%) abstained completely from opioids during weeks 9–12 of Phase 2 (i.e., while still taking buprenorphine-naloxone),
while 61 of 180 SMM patients (33.9%) achieved that outcome (p=0.25). At week 24, 8 weeks after completing the buprenorphine-naloxone taper, only 13 of 180 SMM+ODC patients (7.2%) had been abstinent from opioids during the previous 4 weeks, as compared to 11 of 180 SMM patients (6.1%; p=0.59). The rate of complete abstinence from opioids was significantly higher at week 12 than at week 24 (36.4% vs. 6.7%, p<0.0001).

Urine tests corroborated these results: the rate of opioid-positive urine tests in Phase 2 was significantly higher during the combined taper and post-taper periods (weeks 13–24) than while maintained on buprenorphine-naloxone during weeks 1–12 (58.1% vs. 39.1%, p<0.001).

Impact of chronic pain and lifetime heroin use on opioid use outcomes

As a planned secondary analysis, we examined the impact of the two Phase 1 stratification variables on the primary endpoints. 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 with chronic pain (7.9%) achieved success in Phase 1, compared with 13 of 274 (4.7%) without chronic pain (p=0.25). Seventy-nine of 149 Phase 2 patients with chronic pain (53.0%) achieved success at week 12, compared with 98 of 211 patients (46.4%) without chronic pain (p=0.25).

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 on buprenorphine-naloxone (37.0% vs. 53.8%, p=0.002). A history of any heroin use did not affect Phase 1 outcomes (6.0% (9/150) vs. 6.8% (34/503)) success rates for those with and without heroin use histories, respectively). There was no interaction between either of these two factors and study treatment.

Adverse events

In Phase 1, most patients (n=542, 83.0%) experienced one or more adverse events, most commonly headache (n=191, 29.2%), constipation (n=104, 15.9%), and insomnia (n=86, 13.2%); few (n=15, 2.3%) discontinued treatment as a result of an adverse event. In Phase 2, most patients (n=216, 60.0%) experienced one 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.

Discussion

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

Our findings suggest that physicians can successfully treat many patients dependent upon prescription opioids, with or without chronic pain, using buprenorphine-naloxone with relatively brief weekly medical management visits; half of our sample did well during this 12-week regimen. Consistent with results from a previous study 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. Like 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 treating opioid dependence with buprenorphine see patients as often as weekly. Conversely, more frequent opioid drug counseling, 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, e.g., contingency management, might improve outcomes in this population, given that approximately half of those receiving buprenorphine-naloxone stabilization did not achieve successful outcomes.

The length of our trial may have influenced our results as well. Studies of methadone maintenance treatment with heroin dependent patients have shown that patients who participate in longer-term treatment (e.g., 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 of time. Moreover, it is unclear whether a taper following longer treatment with buprenorphine-naloxone would yield a better outcome.

Our finding regarding the substantial drop in the rate of successful outcomes in Phase 2 that occurred following 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.

Interestingly, the presence of chronic pain did not influence opioid use outcomes. Chronic pain is highly prevalent in patients dependent upon prescription opioids and was present in nearly half of our 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 our 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 appear to respond poorly to addiction treatment except in the context of opioid maintenance therapy. This was the first study, however, to examine this topic prospectively in a population comprised exclusively of those dependent upon prescription opioids. The negative prognostic impact of even minimal lifetime heroin use on outcome while maintained on buprenorphine-naloxone was notable, especially since we excluded those 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.

Strengths of the study include the large, national, multi-site study sample and the broad inclusion criteria, including patients both with and without chronic pain. Consistent with...
other opioid dependence treatment studies,\textsuperscript{15, 40} our study was limited by the high dropout rate from Phase 1 to Phase 2, although dropout rate did not vary by treatment condition.

The 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.\textsuperscript{15} with a largely heroin-dependent population, despite the fact that we had a greater contrast in intensity of counseling conditions than that study. This supports the national trend toward treatment of opioid dependence by physicians in office-based practice.\textsuperscript{7} Further, patients dependent upon 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. Our 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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\textbf{References}


Figure 1.
Study Design
1Stratified by presence or absence of a history of heroin use and current chronic pain
2Standard Medical Management; phase 1, week 1: 2 visits; weeks 2 to 4: 1 visit/wk; and
weeks 5 to 8: biweekly visits
3Opioid dependence counseling (ODC); phase 1, Weeks 1 to 4: 2 visits/wk; Weeks 5 to 8:
biweekly visits
4Buprenorphine-naloxone (bup/nx) dose; 8 to 32 mg/d
5Phase 1 primary endpoint: 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
6Stratified by phase 1 counseling condition, that is, SMM or SMM+ODC
7SMM: phase 2. week 1: 2 visits; and weeks 2 to 16: 1 visit/wk
8ODC; phase 2, Weeks 1 to 6; 2 visits/wk; and weeks 7 to 12: 1 visit/wk
9Phase 2 primary endpoint: abstinent from opioids during week 12 (the final week of bu/nx
stabilization) and during at least 2 of the previous 3 weeks (weeks 9–11)
10Phase 2 secondary endpoint: abstinent from opioids during week 24 and during at least 2
of the previous 3 weeks (weeks 21–23)
Figure 2. Randomization, Treatment, and Follow-up of Study Patients

*Reasons (n = 315) for not meeting Inclusion/Exclusion Criteria: not physically dependent on opioids (n = 47); unable to meet study requirements (n = 39); psychotic or psychiatrically unstable (n = 34); not in good general health (n = 32); did not meet DSM-IV criteria for current opioid dependence (n = 32); medical condition made participation medically hazardous (n = 25); no medical clearance from 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); (10) 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 one category of the reasons for non-eligibility;
5 patients who did not meet all inclusion criteria were randomized. ODC indicates opioid dependence counseling; and SMM, standard medical management.
Table 1

Background and Clinical Characteristics by Counseling Condition, at Baseline

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>SMM+ODC (n=329)</th>
<th>SMM (n=324)</th>
<th>Total (N=653)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sociodemographics</strong></td>
<td></td>
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</tr>
<tr>
<td>Female, No. (%)</td>
<td>125 (38.0)</td>
<td>136 (42.0)</td>
<td>261 (40.0)</td>
<td>.30</td>
</tr>
<tr>
<td>Age, mean (sd)</td>
<td>32.9 (10.1)</td>
<td>33.5 (10.3)</td>
<td>33.2 (10.2)</td>
<td>.46</td>
</tr>
<tr>
<td>White race, No. (%)</td>
<td>301 (91.5)</td>
<td>295 (91.3)</td>
<td>596 (91.4)</td>
<td>.94</td>
</tr>
<tr>
<td>Education, mean years (sd)</td>
<td>13.0 (2.0)</td>
<td>13.0 (2.3)</td>
<td>13.0 (2.2)</td>
<td>.86</td>
</tr>
<tr>
<td>Never married, No. (%)</td>
<td>162 (49.2)</td>
<td>164 (50.6)</td>
<td>326 (49.9)</td>
<td>.72</td>
</tr>
<tr>
<td>Employed full-time, No. (%)</td>
<td>210 (63.8)</td>
<td>201 (62.0)</td>
<td>411 (62.9)</td>
<td>.64</td>
</tr>
<tr>
<td><strong>Clinical</strong></td>
<td></td>
<td></td>
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<tr>
<td><strong>Substance use</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Non-opioid substance dependence diagnoses, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Past year</td>
<td>14 (4.3)</td>
<td>11 (3.4)</td>
<td>25 (3.8)</td>
<td>.57</td>
</tr>
<tr>
<td>Lifetime</td>
<td>80 (24.3)</td>
<td>93 (28.7)</td>
<td>173 (26.5)</td>
<td>.20</td>
</tr>
<tr>
<td>Cannabis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Past year</td>
<td>15 (4.6)</td>
<td>19 (5.9)</td>
<td>34 (5.2)</td>
<td>.45</td>
</tr>
<tr>
<td>Lifetime</td>
<td>49 (14.9)</td>
<td>52 (16.0)</td>
<td>101 (15.5)</td>
<td>.68</td>
</tr>
<tr>
<td>Cocaine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Past year</td>
<td>11 (3.3)</td>
<td>11 (3.4)</td>
<td>22 (3.4)</td>
<td>.97</td>
</tr>
<tr>
<td>Lifetime</td>
<td>59 (17.9)</td>
<td>59 (18.2)</td>
<td>118 (18.1)</td>
<td>.93</td>
</tr>
<tr>
<td>Other stimulants</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Past year</td>
<td>6 (1.8)</td>
<td>7 (2.2)</td>
<td>13 (2.0)</td>
<td>.76</td>
</tr>
<tr>
<td>Lifetime</td>
<td>31 (9.4)</td>
<td>40 (12.3)</td>
<td>71 (10.9)</td>
<td>.23</td>
</tr>
<tr>
<td>Sedatives</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Past year</td>
<td>17 (5.2)</td>
<td>23 (7.1)</td>
<td>40 (6.1)</td>
<td>.30</td>
</tr>
<tr>
<td>Lifetime</td>
<td>30 (9.1)</td>
<td>35 (10.8)</td>
<td>65 (10.0)</td>
<td>.47</td>
</tr>
<tr>
<td>None</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Past year</td>
<td>282 (85.7)</td>
<td>268 (82.7)</td>
<td>550 (84.2)</td>
<td>.29</td>
</tr>
<tr>
<td>Lifetime</td>
<td>180 (54.7)</td>
<td>164 (50.6)</td>
<td>344 (52.7)</td>
<td>.30</td>
</tr>
<tr>
<td><strong>Days of substance use, past 30 days, mean (sd)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Opioid analgesics⁶</td>
<td>27.9 (4.3)</td>
<td>28.2 (3.6)</td>
<td>28.1 (4.0)</td>
<td>.33</td>
</tr>
<tr>
<td>Cannabis</td>
<td>5.2 (9.7)</td>
<td>4.5 (9.1)</td>
<td>4.9 (9.4)</td>
<td>.39</td>
</tr>
<tr>
<td>Sedative-hypnotics (non-barbiturate)</td>
<td>3.8 (7.8)</td>
<td>2.7 (8.0)</td>
<td>3.8 (7.9)</td>
<td>.87</td>
</tr>
<tr>
<td>Alcohol</td>
<td>3.3 (6.2)</td>
<td>2.6 (5.8)</td>
<td>3.0 (6.0)</td>
<td>.18</td>
</tr>
<tr>
<td>Amphetamine</td>
<td>0.7 (3.9)</td>
<td>0.4 (2.6)</td>
<td>0.5 (3.3)</td>
<td>.20</td>
</tr>
<tr>
<td>Patient characteristics</td>
<td>SMM+ODC (n=329)</td>
<td>SMM (n=324)</td>
<td>Total (N=653)</td>
<td>p value</td>
</tr>
<tr>
<td>-------------------------</td>
<td>-----------------</td>
<td>-------------</td>
<td>---------------</td>
<td>---------</td>
</tr>
<tr>
<td>Cocaine</td>
<td>0.5 (1.7)</td>
<td>0.5 (2.3)</td>
<td>0.5 (2.0)</td>
<td>.80</td>
</tr>
<tr>
<td>Barbiturates</td>
<td>0.1 (1.2)</td>
<td>0.3 (2.6)</td>
<td>0.2 (2.0)</td>
<td>.19</td>
</tr>
<tr>
<td>Heroin</td>
<td>0.2 (0.7)</td>
<td>0.1 (0.4)</td>
<td>0.1 (0.6)</td>
<td>.07</td>
</tr>
<tr>
<td>&gt;1 drug</td>
<td>10.6 (11.2)</td>
<td>10.4 (11.4)</td>
<td>10.5 (11.3)</td>
<td>.83</td>
</tr>
<tr>
<td>Ever used heroin, No. (%)</td>
<td>74 (22.5)</td>
<td>76 (23.5)</td>
<td>150 (23.0)</td>
<td>.77</td>
</tr>
<tr>
<td>Years of opioid use, mean (sd)</td>
<td>4.8 (4.3)</td>
<td>5.5 (5.1)</td>
<td>5.2 (4.7)</td>
<td>.08</td>
</tr>
<tr>
<td>Prior opioid use disorder treatment, No. (%)</td>
<td>99 (30.1)</td>
<td>111 (34.3)</td>
<td>210 (32.2)</td>
<td>.25</td>
</tr>
<tr>
<td><strong>Pain</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current chronic pain, No. (%)</td>
<td>139 (42.2)</td>
<td>135 (41.7)</td>
<td>274 (42.0)</td>
<td>.88</td>
</tr>
<tr>
<td>Severity,(^c) mean (sd)</td>
<td>4.4 (2.2)</td>
<td>4.4 (2.1)</td>
<td>4.4 (2.2)</td>
<td>.95</td>
</tr>
<tr>
<td>Interference with general activities,(^c) mean(sd)</td>
<td>4.2 (2.6)</td>
<td>4.2 (2.7)</td>
<td>4.2 (2.7)</td>
<td>.85</td>
</tr>
</tbody>
</table>

\(^a\) Never married: SMM+ODC (n=238), SMM (n=323), Total (N=651)

\(^b\) Most commonly used opiate analgesics past 30 days: oxycodone, extended-release 35.2%; hydrocodone 32.3%; oxycodone, immediate-release 18.7%; methadone 6.4%; morphine 2.1%; other 5.3%

\(^c\) Brief Pain Inventory for n=274 with chronic pain; range=0–10
<table>
<thead>
<tr>
<th>Period</th>
<th>SMM Observed % (n) [95% CI]</th>
<th>SMM+ODC Observed % (n) [95% CI]</th>
<th>GEE model-based results</th>
<th>OR [95% CI]</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>End of Phase 1</td>
<td>7.4 (24/324) [4.8,10.8]</td>
<td>5.8 (19/329) [3.5,8.9]</td>
<td></td>
<td>1.3b [0.7, 2.4]</td>
<td>0.36</td>
</tr>
<tr>
<td>Phase 2, end of treatment</td>
<td>46.7 (84/180) [39.2,54.2]</td>
<td>51.7 (93/180) [44.1,59.2]</td>
<td></td>
<td>0.8c [0.5, 1.2]</td>
<td>0.27</td>
</tr>
<tr>
<td>Phase 2, 8-week post-treatment follow-up</td>
<td>7.2 (13/180) [3.9,12.0]</td>
<td>10.0 (18/180) [6.0,15.3]</td>
<td></td>
<td>0.7c [0.3, 1.3]</td>
<td>0.22</td>
</tr>
</tbody>
</table>

SMM = Standard Medical Management; ODC = Opioid Drug Counseling; CI = Confidence Interval; OR = Odds Ratio; GEE = generalized estimating equations

*aReference category = SMM+ODC

*bAdjusted for chronic pain at baseline and lifetime history of heroin use

*cAdjusted for chronic pain at baseline, lifetime history of heroin use, and Phase 1 randomization
Table 3
Successful Opioid Use Outcome by the Phase 2 Period

<table>
<thead>
<tr>
<th>Phase 2 period</th>
<th>Observed % (n)</th>
<th>[95% CI]</th>
<th>OR [95% CI]</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>End of treatment</td>
<td>49.2 (177/360)</td>
<td>[43.9,54.5]</td>
<td>10.6b [7.2,15.6]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>8-week post-treatment follow-up</td>
<td>8.6 (31/360)</td>
<td>[5.9,12.0]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CI = Confidence Interval; OR = Odds Ratio; GLMM = generalized linear mixed model

bReference category = 8-week post-treatment follow-up