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Sublingual Buprenorphine-Naloxone Compared With Injection Naltrexone for Opioid Use Disorder: Potential Utility of Patient Characteristics in Guiding Choice of Treatment

Edward V. Nunes Jr., M.D.,
Jennifer M. Scodes, M.S.,
Martina Pavlicova, Ph.D.,
Joshua D. Lee, M.D., M.Sc.,
Patricia Novo, M.P.A., M.P.H.,
Aimee N.C. Campbell, Ph.D.,
John Rotrosen, M.D.

New York State Psychiatric Institute and Columbia University Irving Medical Center, New York (Nunes, Scodes, Campbell); Department of Biostatistics, Columbia University Mailman School of Public Health, New York (Pavlicova); and New York University Grossman School of Medicine, New York (Lee, Novo, Rotrosen)

Abstract

Objective: Sublingual buprenorphine-naloxone and extended-release injection naltrexone are effective treatments, with distinct mechanisms, for opioid use disorder. The authors examined whether patients' demographic and clinical characteristics were associated with better response to one medication or the other.

Methods: In a multisite 24-week randomized comparative-effectiveness trial of assignment to buprenorphine-naloxone (N=287) compared with extended-release naltrexone (N=283) comprising inpatients planning to initiate medication treatment for opioid use disorder, 50 demographic and clinical characteristics were examined as moderators of the effect of medication assignment on relapse to regular opioid use and failure to initiate medication. Moderator-by-medication interactions were estimated using logistic regression with correction for multiple testing.

Results: In the intent-to-treat sample, patients who reported being homeless had a lower relapse rate if they were assigned to receive extended-release naltrexone (51.6%) compared with buprenorphine-naloxone (70.4%) (odds ratio=0.45, 95% CI=0.22, 0.90); patients who were not homeless had a higher relapse rate if they were assigned to extended-release naltrexone (70.9%) compared with buprenorphine-naloxone (53.1%) (odds ratio=2.15, 95% CI=1.44, 3.21). In the subsample of patients who initiated medication, the interaction was not significant, with a similar pattern of lower relapse with extended-release naltrexone (41.4%) compared with buprenorphine (68.6%) among homeless patients (odds ratio=0.32, 95% CI=0.15, 0.68) but less difference among those not homeless (extended-release naltrexone, 57.2%; buprenorphine, 52.0%; odds ratio=1.24,

Send correspondence to Dr. Nunes (edward.nunes@nyspi.columbia.edu).

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95% CI=0.80, 1.90). For failure to initiate medication, moderators were stated preference for medication (failure was less likely if the patient was assigned to the medication preferred), parole and probation status (fewer failures with extended-release naltrexone for those on parole or probation), and presence of pain and timing of randomization (more failure with extended-release naltrexone for patients endorsing moderate to severe pain and randomized early while still undergoing medically managed withdrawal).

Conclusions: Among patients with opioid use disorder admitted to inpatient treatment, homelessness, parole and probation status, medication preference, and factors likely to influence tolerability of medication initiation may be important in matching patients to buprenorphine or extended-release naltrexone.

The opioid epidemic continues to inflict enormous morbidity, mortality, and societal costs (1). Medications for opioid use disorder, which include methadone, buprenorphine, and the extended-release injection formulation of naltrexone, are effective but underutilized. Most people with opioid use disorder are not in treatment with medication (2–4), and many localities lack services offering these treatments (5). Methadone, a full mu-opioid receptor agonist, is restricted to specially licensed clinics, while buprenorphine and extended-release naltrexone can be widely prescribed and are well suited for dissemination across primary care, mental health, and addiction settings. Buprenorphine, a mu-opioid receptor partial agonist, is approved by the U.S. Food and Drug Administration (FDA) for the treatment of opioid use disorder. Buprenorphine can be initiated in a patient who is actively using illicit opioids, provided that the patient can abstain from opioids long enough (on the order of hours) to begin to manifest opioid withdrawal symptoms. Naltrexone, a mu-opioid receptor antagonist, is more difficult to initiate because the patient must be fully withdrawn from opioids before the first dose is given to avoid precipitated withdrawal. Therefore, extended-release injection naltrexone is FDA approved for prevention of relapse to opioid use disorder following withdrawal from opioids.

Insurance claims data show that compared with methadone and buprenorphine, naltrexone is least utilized with short durations of treatment, which raises questions about its pragmatic effectiveness (4, 6, 7). However, two recent clinical trials found that buprenorphine and extended-release naltrexone were close in effectiveness (8, 9). In a trial conducted in Norway among patients with opioid use disorder who had completed withdrawal from opioids and were thus ready to initiate naltrexone (8), extended-release naltrexone was noninferior to sublingual buprenorphine-naloxone on the co-primary outcomes of retention in treatment (70% of patients assigned to extended-release naltrexone and 68% assigned to buprenorphine-naloxone completed 12 weeks of treatment) and number of opioid-negative urine tests. In the Extended-Release Naltrexone Versus Buprenorphine-Nalox-one for Opioid Relapse Prevention (X:BOT) trial (9), which was conducted in the United States in patients with opioid use disorder admitted to inpatient units, assignment to extended-release naltrexone was associated with a significantly higher rate of relapse to regular opioid use (65%) compared with buprenorphine-naloxone (57%) over the 24-week trial, a difference accounted for mainly by relapse among patients who failed to complete withdrawal from opioids and thus failed to initiate naltrexone. Substantial dropout and relapse with both medications in these and other studies (3, 10–12) raise the question of whether effectiveness

could be improved by personalizing care, identifying patient characteristics that may guide the choice of the best treatment for each individual.

Here we report what is, to our knowledge, the first systematic analysis of patient-treatment matching for buprenorphine compared with extended-release naltrexone. We examined a panel of demographic and clinical characteristics as moderators of treatment outcome in the X:BOT trial. The X:BOT study comprised 570 patients with opioid use disorder who were admitted to medically managed inpatient programs and consented to random assignment to either buprenorphine-naloxone sublingual film or extended-release injection naltrexone for a 24-week trial (9, 13). As expected, an “induction hurdle” was observed mainly for the group assigned to extended-release naltrexone; 28% of patients failed to initiate extended-release naltrexone, compared with 6% for buprenorphine-naloxone, and most who failed to initiate medication relapsed (9). We therefore first present moderators on the primary outcome of relapse to opioid use over the 24-week trial in the intent-to-treat sample of all randomly assigned patients, with outcome as a function of both medication initiation and clinical course after initiation. This analysis reflects the clinical frame of reference before choice of medication is made, addressing the key pragmatic question of what baseline features may guide choice of medication to optimize long-term outcome. We then present moderators of failure to initiate medication, which is important given the poor outcome for patients with opioid dependence discharged from controlled settings without medication (14–16), and moderators of relapse in the per protocol subsample of patients who successfully initiated medication.

METHODS

Design Overview

The X:BOT trial, conducted in the National Drug Abuse Treatment Clinical Trials Network, was an eight-site 24-week open-label randomized trial comparing the effectiveness of buprenorphine-naloxone (N=287) with extended-release naltrexone (N=283) for prevention of relapse among patients with opioid use disorder who were admitted to inpatient programs. The study design, rationale (13, 17), and primary outcomes have been reported previously (9). Briefly, the study sites were community-based programs providing short-term inpatient treatment followed by outpatient treatment for substance use disorders. Patients were recruited during the inpatient admission and were eligible for the trial if they were ≥18 years old, spoke English, and met DSM-5 criteria for current opioid use disorder. Exclusion criteria were minimized to enhance representativeness and included serious medical or psychiatric conditions or other constraints that made trial participation unwise, including methadone maintenance at ≥30 mg/day, chronic pain requiring opioid therapy, or legal status precluding study completion, such as impending incarceration. Other forms of legal supervision, such as parole or probation, were not exclusionary. All sites obtained institutional review board approval, and all participants provided written informed consent.

As soon as participants provided consent and were determined to be eligible, they were randomly assigned (1:1) to receive buprenorphine-naloxone or extended-release naltrexone, stratified by site and by severity of opioid use disorder, with high severity operationalized as intravenous use of at least six bags per day. The assigned medication was started as

soon as clinically possible after randomization. Buprenorphine-naloxone was initiated after patients had been off opioids long enough to manifest withdrawal symptoms and tolerate a test dose of buprenorphine-naloxone. The first injection of extended-release naltrexone was given after patients had completed medically managed withdrawal and a washout period (typically at least 5–7 days from the last opioid dose), produced a urine sample negative for opioids, and passed a naloxone challenge. The eight inpatient units differed in their approaches to medically managed withdrawal: two used no opioids, only clonidine or other nonopioid medications; four used 3-day to 5-day methadone tapers; and two used 3-day to 14-day buprenorphine tapers. Timing of consent and randomization could occur at any time during the inpatient stay. Thus, some patients were randomly assigned early, during methadone or buprenorphine tapers, while others were randomly assigned after withdrawal had been completed.

Participants were followed for 24 weeks after randomization, and medication management counseling was provided by the physician or nurse overseeing the study medication, as well as outpatient counseling recommended by the treatment program. Buprenorphine-naloxone was adjusted from 8 mg to 24 mg per day as clinically indicated. Extended-release naltrexone was administered by intramuscular injection every 28 days. Participants were compensated $50 for major assessment points and $20 for weekly assessments, for total possible earnings of $710.

Outcome Measures

The primary outcome measure was relapse, reflecting either return to regular opioid use or dropout from treatment. At weekly visits, self-reported substance use data were collected using the timeline follow-back method (18), and urine was tested for opioids (buprenorphine, methadone, morphine [i.e., heroin, codeine, morphine], and oxycodone) and other drugs. Relapse was operationalized as ≥4 consecutive weeks of any nonstudy opioid use (by urine toxicology, selfreport, or failure to provide a urine sample) or ≥7 consecutive days of self-reported nonstudy opioid use. The primary outcome analysis examined time to relapse (9). In this moderator analysis, relapse was dichotomized (relapse compared with no relapse across the 24-week trial), with absence of relapse conceptualized as an indicator of good clinical response.

Failure to initiate study medication (binary: yes/no) was scored if the patient never received a single dose of study medication.

Moderator Variables Measured at Baseline Assessment

Moderator variables were items from patients' medical and psychiatric history, the timeline follow-back (18), the Addiction Severity Index (19), the Hamilton Depression Rating Scale (20), the EuroQol EQ-5D-3L (21), and the Subjective Opioid Withdrawal Scale (22), as well as items created for this study (Table 1). In addition to demographic characteristics, patient characteristics with potential prognostic significance were selected on the basis of the literature or clinical experience, including current severity and characteristics of opioid and other substance use (23–26), history of past treatments for opioid use disorder (26, 27), current psychiatric disorders (26, 28, 29), pain, legal status, current living situation, friends

or family members who use substances (30), medication preference, previous withdrawal discomfort, and randomization timing (early [within 3 days of last exposure to any opioids, including prescribed opioids] compared with late [>3 days after last opioid exposure]).

Data Analysis

For each moderator variable, a logistic regression model was fitted, modeling relapse over the 24-week trial (yes/no) as a function of the moderator variable, treatment assignment (buprenorphine-naloxone compared with extended-release naltrexone), and the moderator-by-treatment interaction, controlling for site as a random effect. The interaction term addressed whether different levels of a moderator variable were associated with differences in the effect of medication assignment on relapse outcome. Treatment effect odds ratios (extended-release naltrexone compared with buprenorphine-naloxone) and their 95% confidence intervals, as well as model-estimated relapse rates, were computed for each level of the moderator if the moderator was categorical, or they were computed at the mean and ±1 standard deviation from the mean if the moderator was continuous. Analogous models were fitted on the outcome of failure to initiate study medication.

All statistical tests were two-sided. In order to maintain an overall significance level of 5%, given the large number of moderator variables, the threshold for considering a moderator effect significant was set at a p value of 0.001 using a Bonferroni correction for 50 moderators (0.05/50=0.001). Moderator variables that fell in the range of $0.001 \leq p < 0.05$ were tabulated for descriptive purposes. A full summary of all moderator-by-treatment group interactions is provided in the online supplement. All analyses were run using SAS, version 9.4 (SAS Institute, Cary, N.C.)

RESULTS

Patient Characteristics

The values of the moderator variables for each treatment group are presented in Table 1. The sample (N=570) was predominantly White and male, with an average age in the early 30s. More than half of participants had a high school education or less, more than half were unemployed, and 25% were homeless. The majority of participants were heroin and intravenous drug users, with an average of 12 years of opioid use. Ninety percent were current cigarette smokers, and more than half were using cannabis. Other substance use and substance use disorders were common, including cocaine, amphetamines, and sedative-hypnotics. Sixty-seven percent of participants had a history of a nonsubstance psychiatric disorder, and 69% endorsed moderate to extreme anxiety or depression on the EQ-5D-3L assessment of quality of life subscale. Only 13% endorsed chronic pain lasting ≥6 months on the medical history form, although more than half endorsed current moderate to extreme physical pain on the EQ-5D-3L. The majority of participants endorsed having friends or family who used opioids or other illicit drugs. Regarding health insurance, 62% (N=356) of participants had Medicaid or Medicare, 10% (N=58) had private insurance, and 27% (N=156) were uninsured.

Moderators of 24-Week Relapse

Interactions of moderator variables by treatment group with a p value <0.05 in the intent-to-treat sample of all randomly assigned patients (N=570) are presented in Table 2, showing the odds ratios and 95% confidence intervals for the treatment effects on relapse and the model-estimated proportions of randomly assigned participants who met relapse criteria within each level of the moderator variable. A significant interaction means that the odds ratios for the treatment effect differ significantly between the levels of a moderator variable. Odds ratios <1.0 indicate lower odds of relapse for patients assigned to extended-release naltrexone compared with buprenorphine-naloxone, and odds ratios >1.0 indicate lower odds of relapse for patients assigned to buprenorphine-naloxone compared with extended-release naltrexone.

Homelessness—assessed as an affirmative response to the question “Are you currently homeless or living in a shelter?”—was the only moderator that was significant at a p value <0.001. Among homeless patients, the estimated relapse rate was lower among those assigned to extended-release naltrexone (51.6%) compared with buprenorphine-naloxone (70.4%) (odds ratio=0.45, 95% CI=0.22, 0.90), whereas among patients who were not homeless, the estimated relapse rate was lower in the buprenorphine-naloxone group (53.1%) compared with the extended-release naltrexone group (70.9%) (odds ratio=2.15, 95% CI=1.44, 3.21).

Moderator-by-treatment interactions with a p value <0.05 for the outcome of relapse in the per protocol subsample of patients who successfully initiated medication (N=474) are summarized in Table 3. No moderators were significant at a p value <0.001. Homelessness (interaction, p=0.002) showed a pattern similar to that of the intent-to-treat sample, with a lower relapse rate with extended-release naltrexone (41.4%) compared with buprenorphine (68.6%) (odds ratio=0.32, 95% CI=0.15, 0.68) among homeless patients, although less difference between medications among those not homeless was observed. Relapse rates were lower overall in the per protocol sample because patients who failed to initiate medication and who subsequently relapsed were selected out. This had a greater effect in the extended-release naltrexone group because of the higher initiation failure rate (28%) compared with the buprenorphine group (6%).

Moderators of Failure to Initiate Study Medication

Moderator-by-treatment interactions with a p value <0.05 for the outcome of failure to initiate study medication are presented in Table 4. Odds ratios >1.0 indicate a greater likelihood of failure among patients assigned to extended-release naltrexone compared with buprenorphine-naloxone. The point estimates of the odds ratios vary in magnitude but are all >1, reflecting the overall lower likelihood of successful initiation with extended-release naltrexone. The overall rate of failure to initiate with extended-release naltrexone was 27.9% (N=79/283), compared with 5.9% (N=17/287) with buprenorphine-naloxone.

Four variables had significant interactions with treatment assignment (p<0.001): current probation or parole, preference for treatment with buprenorphine-naloxone, moderate to severe pain endorsed on the EQ-5D-3L, and timing of randomization. Patients on probation

or parole had similar estimated rates of failure to initiate extended-release naltrexone (17.4%) and buprenorphine-naloxone (14.4%) (odds ratio=1.25, 95% CI=0.43, 3.61), whereas among those not on parole or probation, the estimated failure rate was higher if they were assigned to extended-release naltrexone (27.0%) compared with buprenorphine-naloxone (2.8%) (odds ratio=12.86, 95% CI=5.96, 27.76).

Among patients who endorsed the statement “I would prefer to receive buprenorphine-naloxone,” only one patient (model-estimated proportion, 0.88%) failed to initiate buprenorphine-naloxone, while there was a relatively higher estimated rate of failure to initiate extended-release naltrexone (33.0%; odds ratio=55.28, 95% CI=7.27, 420.15). Among those who endorsed disagreement with a preference for buprenorphine-naloxone, the failure rate for initiating extended-release naltrexone (17.5%) was closer to that for buprenorphine-naloxone (12.9%) (odds ratio=1.43, 95% CI=0.59, 3.44).

Participants who endorsed current moderate to severe physical pain had a relatively higher estimated rate of failure to initiate extended-release naltrexone (32.4%) compared with buprenorphine-naloxone (2.0%) (odds ratio=23.68, 95% CI=8.21, 68.34), while among those who did not endorse pain, there was a lower estimated failure rate among those who were assigned to extended-release naltrexone (16.4%), which was closer to the failure rate for buprenorphine-naloxone (8.3%) (odds ratio=2.18, 95% CI=1.04, 4.60).

Early randomization (within 3 days of the last opioid exposure) was associated with a much higher rate of failure to initiate extended-release naltrexone (41.3%) compared with buprenorphine-naloxone (1.5%) (odds ratio=47.79, 95% CI=11.15, 204.89), whereas late randomization (>3 days since the last opioid exposure) was associated with lower failure to initiate extended-release naltrexone (17.0%), which was closer to the buprenorphine-naloxone failure rate (8.3%) (odds ratio=2.26, 95% CI=1.15, 4.45).

DISCUSSION

We evaluated characteristics of patients entering inpatient treatment for opioid use disorder as moderators of relapse outcome in a trial comparing assignment to one of two efficacious medications: sublingual buprenorphine-naloxone or extended-release injection naltrexone. These medications differ in pharmacodynamics, receptor binding (mu-opioid receptor partial agonist [buprenorphine] versus antagonist [extended-release naltrexone]), pharmacokinetics (with extended-release naltrexone having a month-long duration of action), and ease of initiation (with naltrexone having a substantial induction hurdle). Across a panel of moderator variables, including many that may be considered inherent characteristics of patients, such as demographic characteristics or indicators of severity of substance use or cooccurring disorders, the one significant moderator of 24-week relapse in the intent-to-treat sample was a social determinant, homelessness (Table 2). Patients who reported being homeless were less likely to relapse if they were assigned to extended-release naltrexone compared with buprenorphine-naloxone, while for those who were not homeless, relapse was less likely if they were assigned to buprenorphine-naloxone.

The moderation effect of homelessness should be interpreted in light of the study design, whereby patients were randomly assigned to medication conditions as soon as they were ready to make a treatment plan but in many cases before they were physiologically ready to start naltrexone. This design was chosen to reflect real-world clinical practice, where buprenorphine is easily initiated, whereas naltrexone requires detoxification (17). The intent-to-treat sample reflects the pragmatic clinical juncture before choice of medication is made, when a moderator could inform the choice. However, homelessness should be understood as a moderator of the composite of medication assignment, initiation, and exposure, and it is not possible to attribute the moderator effect of homelessness solely to medication exposure. Homelessness was not a significant moderator of failure to initiate medication. In the per protocol subsample of patients who initiated medication, homelessness was no longer a significant moderator of relapse outcome (Table 3). The pattern was similar among the homeless patients, with less relapse with extended-release naltrexone compared with buprenorphine-naloxone, although there was less difference between medications among those who were not homeless. Patients who failed to initiate medication, most of whom relapsed, were selected out of the per protocol sample, resulting in lower relapse rates with extended-release naltrexone across both those who were homeless and those who were not homeless.

Homelessness is a highly stressful circumstance, often associated with other challenging stressors (e.g., unemployment or underemployment, psychiatric disorders, limited social capital), and it creates an unstable, possibly chaotic, living situation. Thus, homelessness could make it more difficult to adhere to a daily medication regimen, as has been observed with adherence to antiretroviral and antipsychotic medications (31–33), while a long-acting injection could afford a potential advantage. One previous study suggested the utility of extended-release naltrexone among indigent populations with heavy drinking (34). Extended-release injectable buprenorphine (35, 36) and naltrexone implants (37, 38) have shown efficacy and are increasingly available. More research is needed on how best to engage and support patients with opioid use disorder who are homeless or otherwise under challenging social circumstances, including on the potential utility of long-acting formulations of medications for opioid use disorder.

Significant moderators of failure to initiate medication included another social circumstance, being on parole or probation, which was carried by a relatively higher buprenorphine-naloxone initiation failure rate and a lower extended-release naltrexone failure rate among patients on probation or parole (Table 4). This may reflect the stigma and discrimination against agonist or partial agonist treatment in criminal justice settings, where naltrexone, as an antagonist, may be favored by officials and providers, and patients may feel pressure to initiate and adhere to it (39).

Patients' stated preference for buprenorphine-naloxone moderated initiation failure. Medication preferences were about evenly distributed between buprenorphine-naloxone, extended-release naltrexone, and no strong preference. Patients who endorsed a preference for buprenorphine-naloxone had a higher initiation failure rate on extended-release naltrexone and a low failure rate on buprenorphine-naloxone. Patients' beliefs about the efficacy and safety of the medications for opioid use disorder, possibly based on past

experience, and whether a medication is believed to be consistent with the goal of being "drug free," have been shown to be associated with choice of whether to take medication and which medication to take (40). This suggests the importance of incorporating patients' preferences and beliefs into shared decision making around choice of medication, informed by discussion of differences in mechanism, dosing and expected effects, and a patient's past experiences with treatments.

The other significant moderators of initiation failure were current moderate to severe pain and early randomization within 3 days of the last opioid dose, associated with low failure rates with buprenorphine-naloxone and higher failure rates with extended-release naltrexone. Early randomization meant that the patient had to endure more withdrawal symptoms before naltrexone could be started. Taken together with similar patterns at a p value <0.05 observed for anxiety and depression and high discomfort during past episodes of opioid withdrawal, these may reflect factors that make the opioid withdrawal involved in initiating naltrexone more difficult to tolerate, favoring buprenorphine-naloxone. Buprenorphine, as a mu-opioid receptor partial agonist, relieves withdrawal symptoms and pain. For patients aiming toward extended-release naltrexone, expected withdrawal severity or difficulty tolerating the withdrawal process should be considered in deciding whether to medicate withdrawal symptoms more aggressively, conduct withdrawal more gradually, or pivot the treatment plan toward stabilization on buprenorphine or methadone. Patients with opioid use disorder who leave inpatient or residential settings or incarceration without being started on medication are at high risk of relapse (14) and overdose (15, 16). Among patients who failed to initiate medication in our study, almost all relapsed, and this group accounted for almost half of the overdoses observed over the follow-up period (9). Thus, the priority should be to ensure that one of the effective medications is started before discharge (14, 41–43).

Strengths of this moderator analysis include a rigorously conducted comparative effectiveness trial, a comprehensive set of moderator variables, correction for multiple statistical tests, and a large sample size. However, limitations on generalizability need to be considered. The sample was predominantly uninsured or publicly insured, unemployed, and with limited educational attainment, characteristic of patients presenting to publicly funded clinics. Additionally, the sample was predominantly male and Caucasian. While representative of national samples (44), this highlights the need for further work that includes adequate representation of women and often underrepresented racial and ethnic groups to conduct meaningful analyses. Patients were recruited from inpatient units, a clinically important population, because many people with opioid use disorder seek inpatient or residential treatment and may be a more severely ill group. As previously discussed, randomization occurred when patients were ready to make a plan for medication but often not physiologically ready to start medication, particularly naltrexone. This reflects real-world practice on short-term inpatient units, but the findings may not generalize to patients already fully detoxified and ready to initiate either buprenorphine or naltrexone, as might be encountered during discharge planning at longer-term residential treatment settings or before release from jail or prison. The sites employed a range of methods for medically managed withdrawal, and buprenorphine maintenance doses varied according to clinical judgment. These, again, reflect real-world practice, but naltrexone initiation methods may not have

been optimized, and higher doses might have improved outcomes with buprenorphine. Finally, it is important to recognize the limitations of a moderator analysis, namely, that it identifies patterns of treatment response across a population of patients but does not generate individual-level predictions of treatment response.

In summary, although extended-release naltrexone and buprenorphine-naloxone are mechanistically different medications for treatment of opioid use disorder, only one patient characteristic, homelessness, was found to be a significant moderator of relapse over this 24-week comparative effectiveness trial. Homeless patients were less likely to relapse if they were assigned to extended-release naltrexone, and those who were not homeless were less likely to relapse if they were assigned to buprenorphine-naloxone. This suggests a potential advantage for a long-acting injectable formulation of medication for patients living in circumstances where adherence to daily buprenorphine-naloxone may be a challenge. Moderators of failure to initiate medication included another common social determinant of health, criminal justice involvement, as well as stated preference for medication and characteristics, including early randomization and pain, that are likely to make naltrexone initiation more uncomfortable than buprenorphine initiation. Differences between moderators of 24-week relapse compared with initiation failure highlight that these are separate challenges, and further work is needed both to improve naltrexone initiation and to reduce dropout from medication treatments and relapse over the long term. The pragmatic implications are that social circumstances likely to affect adherence to medication, the likelihood of tolerating withdrawal from opioids and naltrexone initiation, and a patient's preferences should be considered in helping to determine the choice of medication for treatment of opioid use disorder.

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TABLE 1.

Demographic and clinical characteristics examined as moderator variables among all patients randomly assigned to extended-release naltrexone or buprenorphine-naloxone (N=570)[a]

Moderator Variable	Extended-Release Naltrexone (N=283)		Buprenorphine-Naloxone (N=287)	
	N	**%**	**N**	**%**
Male	195	68.9	206	71.8
	Mean	**SD**	**Mean**	**SD**
Age (years)	34.0	9.5	33.7	9.8
	N	**%**	**N**	**%**
Age ≤25 years	49	17.3	62	21.6
Hispanic ethnicity	45	15.9	54	18.8
Race				
Caucasian	206	72.8	215	74.9
African American	29	10.2	28	9.8
Other	48	17.0	44	15.3
Education				
Less than high school	63	22.3	69	24.0
High school or GED	94	33.2	96	33.4
Greater than high school	126	44.5	122	42.5
Not employed	179	63.3	181	63.1
Opioid use				
Primary opioid				
Opioid analgesics	43	15.8	47	16.8
Heroin	230	84.2	233	83.2
Any current heroin use	248	87.6	251	87.5
Any current intravenous use	189	66.8	196	68.3
Current methadone prescription[b]	42	14.8	52	18.1
	Mean	**SD**	**Mean**	**SD**
Primary opioid cost (dollars per day)	90.7	76.7	96.3	74.5

Moderator Variable	Extended-Release Naltrexone (N=283)		Buprenorphine-Naloxone (N=287)	
	N	%	N	%
	N	%	N	%
Other current substance use				
Cigarette smoker	250	88.3	263	91.6
Amphetamines	56	19.8	72	25.1
Cocaine/crack	112	39.6	128	44.6
Cannabis	153	54.1	152	53.0
Hallucinogens	8	2.8	12	4.2
DSM-5 substance use disorder				
Alcohol	71	25.1	88	30.7
Amphetamines	42	14.8	64	22.3
Benzodiazepine/other sedative	69	24.4	84	29.3
Cannabis	72	25.4	91	31.7
Cocaine	75	26.5	100	34.8
	Mean	SD	Mean	SD
History of substance use				
Age at onset of nicotine use (years)	15.9	5.3	15.7	4.9
Age at onset of any opioid use (years)	21.2	6.5	21.5	7.6
Age at onset of heroin use (years)	25.0	7.0	24.3	7.9
Duration of opioid use (years)	12.8	8.9	12.2	9.1
	N	%	N	%
Past treatment history				
Current treatment is first treatment in lifetime	100	35.3	109	38.0
Any past treatment was successful[C]	123	43.5	101	35.2
Past methadone or buprenorphine treatment was successful[C]	115	40.6	86	30.0
Past naltrexone treatment was successful	13	4.6	11	3.8
	Mean	SD	Mean	SD
Other psychiatric symptoms or disorders				

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Moderator Variable	Extended-Release Naltrexone (N=283)		Buprenorphine-Naloxone (N=287)	
	N	%	N	%
Hamilton Depression Rating Scale score	8.6	6.5	9.3	6.6
ASI psychiatric domain composite score	0.3	0.2	0.3	0.6
Anxiety or depression, moderate or extreme (EuroQoL)	191	67.5	200	69.7
Any psychiatric disorder[d]	190	67.1	191	66.6
Pain				
Chronic pain longer than 6 months[e]	29	10.3	44	15.3
Pain discomfort, moderate or extreme (EuroQoL)	163	57.6	172	59.9
Criminal justice status: current probation or parole	42	14.9	50	17.4
Living situation				
Current homelessness[f]	74	26.1	69	24.0
Any friends or family with alcohol use problems	131	46.8	155	54.4
Any friends or family with heroin or other opioid use problems	175	62.5	171	60.0
Any friends or family with illicit drug problems	173	61.8	200	70.2
Living with a person with alcohol use disorder	31	11.0	34	11.8
Living with a person using illicit drugs	59	20.8	57	19.9
Medication preference[g]				
No strong medication preference				
Disagree	85	30.1	85	29.6
Neutral	110	39.0	102	35.5
Agree	87	30.9	100	34.8
Prefer to receive buprenorphine-naloxone				
Disagree	68	24.1	73	25.4
Neutral	117	41.5	122	42.5
Agree	97	34.4	92	32.1
Prefer to receive extended-release naltrexone				
Disagree	67	23.8	62	21.6
Neutral	137	48.6	136	47.4
Agree	78	27.7	89	31.0
Opioid withdrawal: typical discomfort level during past episodes of opioid withdrawal				

Moderator Variable	Extended-Release Naltrexone (N=283)		Buprenorphine-Naloxone (N=287)	
	N	**%**	**N**	**%**
0–7 (0=none; 1=little discomfort)	152	53.9	148	51.7
8–10 (10=almost unbearable)	130	46.1	138	48.3
	Mean	**SD**	**Mean**	**SD**
Subjective Opioid Withdrawal Scale (score range, 0–64)	15.6	13.4	15.6	13.2
	N	**%**	**N**	**%**
Timing of randomization				
Early (within 3 days of last opioid exposure)	107	37.8	110	38.3
Late (>3 days since last opioid exposure)	176	62.2	177	61.7
Severity of opioid use				
Low (nonintravenous use or intravenous use at <6 bags/day)	171	60.4	172	59.9
High (intravenous use at ≥6 bags/day)	112	39.6	115	40.1

[a] ASI=Addiction Severity Index; EuroQol=Euro Quality of Life Scale.

[b] Among patients on methadone, only those with prescriptions for <30 mg/day were eligible for the trial.

[c] Patients were asked whether they considered past treatments to be successful (yes or no).

[d] Psychiatric disorders were assessed by clinical history by the medical clinician and included anxiety or panic, attention deficit hyperactivity disorder, bipolar disorder, major depressive disorder, schizophrenia, suicidal ideation, suicidal behavior, psychotic episodes, or other psychiatric disorder.

[e] Chronic pain was assessed by clinical history by the medical clinician.

[f] Homelessness was assessed as an affirmative response to the question “Are you currently homeless or living in a shelter?”

[g] Patients were asked to respond to the following statements: “I do not have a strong preference for which medication I receive”; “I prefer to receive buprenorphine-naloxone”; and “I prefer to receive extended-release naltrexone.”

TABLE 2.

Moderators of medication treatment effect (extended-release naltrexone compared with buprenorphine-naloxone) on relapse (compared with no relapse) across the 24-week trial for the total randomized sample (N=570)

	Total Randomized Sample						
	Treatment-by-Moderator Interaction[a]			Treatment Effect		Estimated Relapse Rate[c] (%)	
Moderator Variable	**F**	**df**	**p**	**Odds Ratio[b]**	**95% CI**	**Extended-Release Naltrexone**	**Buprenorphine-Naloxone**
p<0.001							
Current homelessness[d]	14.59	1, 559	<0.001				
No				2.15	1.44, 3.21	70.86	53.11
Yes				0.45	0.22, 0.90	51.62	70.44
0.001≤p<0.05							
DSM-5 cocaine diagnosis	4.40	1, 559	0.036				
Nonuser/none				1.82	1.20, 2.77	69.62	55.69
Mild, moderate, or severe				0.83	0.45, 1.52	55.16	59.76
Subjective Opioid Withdrawal	4.71	1, 559	0.030				
Scale[e]							
Mild, 2.3				0.98	0.61, 1.60	60.25	60.64
Moderate, 15.6				1.45	1.03, 2.05	66.08	57.28
Severe, 28.8				2.15	1.30, 3.54	71.47	53.85

[a] Logistic regression was conducted, with a p value <0.001 considered significant.

[b] Odds ratios >1.0 favored buprenorphine-naloxone;odds ratios <1.0 favored extended-release naltrexone.

[c] Values are model estimated.

[d] Homelessness was assessed as an affirmative response to the question “Are you currently homeless or living in a shelter?”

[e] For the Subjective Opioid Withdrawal Scale, odds ratios were computed at the mean and ±1 standard deviation of the mean values of scores given that the measure was continuous (mean=15.6, SD=13.3). Scores <11 indicate mild withdrawal; scores 11–20 indicate moderate withdrawal; and scores >21 indicate severe withdrawal.

TABLE 3.

Moderators of medication treatment effect (extended-release naltrexone compared with buprenorphine-naloxone) on relapse (compared with no relapse) across the 24-week trial for the per protocol sample (N=474) who successfully initiated study medication

	Per Protocol Sample						
	Treatment-by-Moderator Interaction[a]			Treatment Effect		Estimated Relapse Rate[d] (%)	
Moderator Variable[b]	F	df	p	Odds Ratio[c]	95% CI	Extended-Release Naltrexone	Buprenorphine-Naloxone
0.001≤p<0.05							
Current homelessness[e]	9.49	1, 463	0.002				
No				1.24	0.80, 1.90	57.20	51.95
Yes				0.32	0.15, 0.68	41.44	68.64
Subjective Opioid Withdrawal	4.42	1, 463	0.036				
Scale[f]							
Mild, 2.3				0.59	0.35, 0.99	46.98	60.15
Moderate, 15.6				0.87	0.60, 1.26	52.71	56.06
Severe, 28.8				1.30	0.77, 2.20	58.38	51.89
Timing of randomization[g]	9.79	1, 463	0.002				
Early				0.37	0.19, 0.72	41.33	65.44
Late				1.33	0.85, 2.10	56.93	49.75

[a] Logistic regression was conducted, with a p value <0.001 considered significant.

[b] There were no moderators with a p value <0.001.

[c] Odds ratios >1.0 favored buprenorphine-naloxone; odds ratios <1.0 favored extended-release naltrexone.

[d] Values are model estimated.

[e] Homelessness was assessed an affirmative response to the question “Are you currently homeless or living in a shelter?”

[f] Odds ratios were computed at the mean and ±1 standard deviation of the mean values of Subjective Opioid Withdrawal Scale scores given that the measure was continuous (mean=15.6, SD=13.3). Scores <11 indicate mild withdrawal; scores 11–20 indicate moderate withdrawal; and scores >21 indicate severe withdrawal.

[g] Early randomization occurred within 3 days of the last opioid exposure, illicit or prescribed; late randomization occurred more than 3 days after the last opioid exposure.

TABLE 4.

Moderators of failure to initiate study medication among patients randomly assigned to extended-release naltrexone (N=283) or buprenorphine-naloxone (N=287)

	Treatment-by-Moderator Interaction[a]			Treatment Effect		Estimated Initiation Failure Rate[c] (%)	
Moderator Variable	**F**	**df**	**p**	**Odds Ratio[b]**	**95% CI**	**Extended-Release Naltrexone**	**Buprenorphine-Naloxone**
p<0.001							
Pain discomfort, moderate or extreme	13.08	1, 559	<0.001				
None				2.18	1.04, 4.60	16.42	8.25
Moderate or extreme				23.68	8.21, 68.34	32.44	1.99
Current probation or parole	12.20	1, 558	<0.001				
No				12.86	5.96, 27.76	27.04	2.80
Yes	7.13	2, 556	<0.001	1.25	0.43, 3.61	17.39	14.39
Prefer to receive buprenorphine-naloxone	7.13	2, 556	<0.001				
Disagree				1.43	0.59, 3.44	17.50	12.94
Neutral				9.22	3.35, 25.39	23.62	3.25
Agree				55.28	7.27, 420.15	33.01	0.88
Timing of randomization[d]	13.93	1, 559	<0.001				
Early				47.79	11.15, 204.89	41.30	1.45
Late				2.26	1.15, 4.45	17.03	8.33
0.001≤p<0.05							
Hispanic ethnicity	3.98	1, 559	0.047				
Not Hispanic				4.88	2.68, 8.89	22.95	5.75
Hispanic				44.49	5.49, 360.56	37.00	1.30
Current cannabis use	4.50	1, 559	0.034				
No				4.09	2.05, 8.19	27.04	8.30
Yes				18.49	5.52, 61.97	24.32	1.71
Any past treatment successful	4.91	1, 559	0.027				
No				4.11	2.13, 7.93	23.49	6.95
Yes				25.03	5.81, 107.87	27.87	1.52
Past methadone or buprenorphine treatment successful	4.16	1, 559	0.042				

Moderator Variable	Treatment-by-Moderator Interaction[a] F	df	p	Treatment Effect Odds Ratio[b]	95% CI	Estimated Initiation Failure Rate[c] (%) Extended-Release Naltrexone	Buprenorphine-Naloxone
No				4.52	2.39, 8.55	25.02	6.87
Yes				40.74	5.40, 307.42	25.75	0.84
Anxiety or depression levels, moderate or extreme	4.38	1, 559	0.037				
None				3.15	1.35, 7.38	21.79	8.12
Moderate or extreme				10.86	4.93, 23.92	27.21	3.33
Any friends or family with heroin or other opioid use problems	4.62	1, 554	0.032				
No				15.88	5.33, 47.27	30.65	2.71
Yes				3.89	1.97, 7.68	21.81	6.69
Prefer to receive extended-release naltrexone:	5.61	2, 556	0.004				
Disagree				28.59	3.65, 224.22	30.23	1.49
Neutral				24.61	5.71, 106.01	23.57	1.24
Agree				2.31	1.07, 4.98	24.54	12.35
Typical discomfort level during past episodes of opioid withdrawal	7.97	1, 557	0.005				
0–7 (0 = none; 1=little discomfort)				3.08	1.48, 6.40	19.65	7.36
8–10 (10=almost unbearable)				19.73	6.80, 57.26	31.64	2.29

[a] Logistic regression was conducted, with a p value <0.001 considered significant.

[b] Odds ratios >1.0 favored buprenorphine-naloxone; odds ratios <1.0 favored extended-release naltrexone.

[c] Values are model estimated.

[d] Early randomization occurred within 3 days of the last opioid exposure, illicit or prescribed; late randomization occurred more than 3 days after the last opioid exposure.