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Compounded Topical Pain Creams to Treat Localized Chronic Pain

A Randomized Controlled Trial

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Background: The use of compounded topical pain creams has increased dramatically, yet their effectiveness has not been well evaluated.

Objective: To determine the efficacy of compounded creams for chronic pain.

Design: Randomized controlled trials of 3 interventions. (ClinicalTrials.gov: NCT02497066)

Setting: Military treatment facility.

Participants: 399 patients with localized pain classified by each patient's treating physician as neuropathic (*n* = 133), nociceptive (*n* = 133), or mixed (*n* = 133).

Interventions: Pain creams compounded for neuropathic pain (ketamine, gabapentin, clonidine, and lidocaine), nociceptive pain (ketoprofen, baclofen, cyclobenzaprine, and lidocaine), or mixed pain (ketamine, gabapentin, diclofenac, baclofen, cyclobenzaprine, and lidocaine), or placebo.

Measurements: The primary outcome measure was average pain score 1 month after treatment. A positive categorical response was a reduction in pain score of 2 or more points coupled with a score above 3 on a 5-point satisfaction scale. Secondary outcomes included Short Form-36 Health Survey scores, satisfaction, and categorical response. Participants with a positive outcome were followed through 3 months.

Results: For the primary outcome, no differences were found in the mean reduction in average pain scores between the treatment and control groups for patients with neuropathic pain (−0.1 points [95% CI, −0.8 to 0.5 points]), nociceptive pain (−0.3 points [CI, −0.9 to 0.2 points]), or mixed pain (−0.3 points [CI, −0.9 to 0.2 points]), or for all patients (−0.3 points [CI, −0.6 to 0.1 points]). At 1 month, 72 participants (36%) in the treatment groups and 54 (28%) in the control group had a positive outcome (risk difference, 8% [CI, −1% to 17%]).

Limitations: Generalizability is limited by heterogeneity among pain conditions and formulations of the study interventions. Randomized follow-up was only 1 month.

Conclusion: Compounded pain creams were not better than placebo creams, and their higher costs compared with approved compounds should curtail routine use.

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Chronic pain affects approximately 31% of the population (1), making it the leading cause of years lost to disability worldwide (2). According to a 2010 analysis, roughly 100 million Americans have chronic pain, which carries an estimated annual cost approaching $600 billion (3). Despite this burden, few reliable treatments exist for chronic pain. First-line medications for chronic pain conditions have large needed-to-treat numbers and are associated with substantial side effects that curtail their use (4). The lack of strong efficacy of nonopioid analgesics for chronic pain is thought to be partially responsible for the opioid epidemic (5). Procedures are often touted as effective means to alleviate pain. Yet, despite the increasing number of surgeries and other interventions targeting chronic pain, the evidence for long-term benefit is weak, and the volume of procedures performed does not correlate with disability rates (6, 7).

The side effects associated with analgesics, including nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids, and the limitations of procedures have led many practitioners to seek alternatives for treating chronic pain (5, 8). One such treatment is topical creams. In a 2001 online survey, 27% of responding physicians reported using compounded pain creams in their practices, a figure that has probably increased as the result of growing awareness (9). One population for whom treatments without central effects may be beneficial is military personnel, because opioid therapy may render a service member nondeployable and medications that affect the central nervous system may have a negative effect on judgment and motor skills. However, the evidence supporting pain creams is weak. Although data support the use of the topical NSAIDs; capsaicin; and to some extent, lidocaine as pain treatments (10–12), the evidence for other analgesics, particularly those that act via central mechanisms (such as ketamine and muscle relaxants) is anecdotal (13–15) or mostly negative (10, 16).

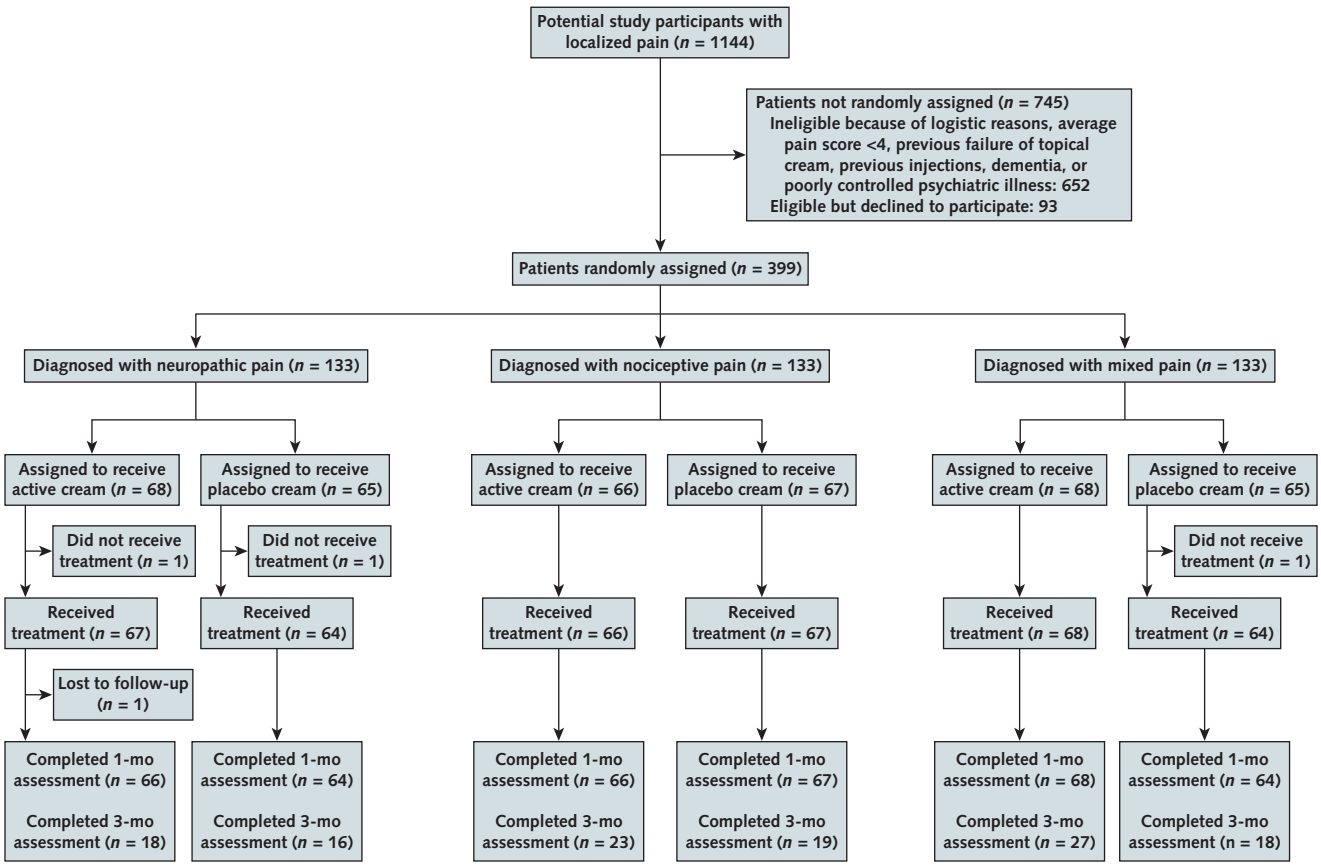
In 2014, the National Defense Authorization Act (H.R. 3304) mandated that the U.S. Government Accountability Office examine the Tricare health system's payments for compounded medications. The office reported that Tricare's pharmacy benefits program paid $259 million for compounded medications in fiscal year 2013 (17). In 2014, the cost increased to $746 million,

See also:

Summary for Patients 2

Web-Only
Supplement

Figure 1. Study flow chart.



and for the first month of 2015, the U.S. Department of Defense (DoD) spent $6 million per day on these medicines. Similar surges for the Centers for Medicare & Medicaid Services, which spent more than a half-billion dollars on topical pain creams for Medicare Part D beneficiaries in 2015, resulted in calls from news organizations for investigations into the prescribing practices and effectiveness of these agents (18). The soaring costs, coupled with sparse efficacy data, prompted the Defense Health Agency to evaluate this issue (19). The objectives of this study were to determine the efficacy of compounded pain creams for chronic pain conditions and whether efficacy differs among various pain classifications. We hypothesized that compared with placebo, compounded topical pain creams would provide greater pain relief and functional improvement.

METHODS

Design Overview

We performed a double-blind, randomized, parallel study comparing active topical pain formulas with placebo creams for 3 types of chronic pain: neuropathic, nociceptive (nonneuropathic), and mixed. (The study protocol is available as a **Supplement** at Annals.org.) Each pain subgroup was randomized separately. Participants, treating physicians, investigators performing follow-ups, and outcome adjudicators were all blinded to allocation. The Walter Reed National Military Medical Center Institutional Review Board approved this study, and all patients provided informed written consent. Participants received treatment between August 2015 and February 2018.

Participants and Setting

The study site was an urban, academic military treatment facility that provides health care to DoD beneficiaries and government officials. A total of 399 participants (133 in each subgroup) were recruited from 2 pain clinics at Walter Reed, via posted advertisements, and from referrals by primary care and specialty clinics. To be included in the study, patients had to be 18 to 90 years old; have localized pain, including in the face, back or buttocks, neck, abdomen, chest, groin, or up to 2 extremities; have an average pain score of 4 or greater on a 0- to 10-point numerical rating scale during the preceding week; and have symptoms lasting longer than 6 weeks. Exclusion criteria were reports of diffuse pain, a previous trial with a topical pain cream, a poorly controlled psychiatric condition, an allergy to any medication contained in the prescribed pain cream, and an inability to understand English.

Table 1. Baseline Characteristics, by Pain Classification and for All Patients

Characteristic	Neuropathic Pain		Nociceptive Pain		Mixed Pain	
	Placebo (*n* = 65)	Drug (*n* = 68)	Placebo (*n* = 67)	Drug (*n* = 66)	Placebo (*n* = 65)	Drug (*n* = 68)
Median age (IQR), *y*	50.0 (41.0–61.0)	57.0 (46.0–67.0)	52.0 (37.0–63.0)	47.0 (33.0–58.0)	51.0 (40.0–65.0)	48.5 (35.5–64.5)
Female sex, *n (%)*	31 (48)	35 (51)	34 (51)	32 (48)	35 (54)	36 (53)
Obesity (BMI ≥30 kg/m^2), *n (%)*	18 (28)	25 (37)	21 (31)	18 (27)	26 (40)	24 (35)
Military status, *n (%)*						
None	37 (57)	49 (72)	33 (49)	33 (50)	40 (62)	37 (54)
Enlisted	20 (31)	14 (21)	23 (34)	21 (32)	16 (25)	20 (29)
Officer	8 (12)	5 (7)	11 (16)	12 (18)	9 (14)	11 (16)
Tobacco use, *n (%)*	4 (6)	3 (4)	5 (7)	5 (8)	8 (12)	5 (7)
Inciting event, *n (%)*						
None	24 (37)	31 (46)	33 (49)	45 (68)	32 (49)	33 (49)
Motor vehicle accident	6 (9)	5 (7)	5 (7)	3 (5)	6 (9)	4 (6)
Fall	3 (5)	3 (4)	5 (7)	4 (6)	3 (5)	4 (6)
Sports	4 (6)	2 (3)	5 (7)	3 (5)	1 (2)	3 (4)
Work	7 (11)	4 (6)	15 (22)	6 (9)	11 (17)	10 (15)
Surgery	15 (23)	17 (25)	2 (3)	2 (3)	11 (17)	13 (19)
Other	6 (9)	6 (9)	2 (3)	3 (5)	1 (2)	1 (1)
Median pain duration (IQR), *y*	3.0 (1.0–7.0)	4.0 (1.0–7.5)	4.0 (1.5–10.0)	3.5 (2.0–6.0)	4.0 (1.3–10.0)	4.3 (2.0–11.0)
Mean average pain score (SD)	5.4 (1.3)	5.7 (1.6)	5.3 (1.2)	5.3 (1.1)	5.8 (1.6)	5.5 (1.3)
Mean worst pain score (SD)	8.0 (1.7)	7.9 (1.8)	7.7 (1.5)	7.5 (1.5)	8.0 (1.5)	7.8 (1.6)
Allodynia, *n (%)*	23 (35)	36 (53)	5 (7)	5 (8)	9 (14)	9 (13)
Opioid use, *n (%)*						
None	51 (78)	56 (82)	57 (85)	58 (88)	45 (69)	50 (74)
Low-dose (<60 MEQ)	12 (18)	9 (13)	10 (15)	6 (9)	15 (23)	13 (19)
High-dose (≥60 MEQ)	2 (3)	3 (4)	0 (0)	2 (3)	5 (8)	5 (7)
Pain location, *n (%)**						
Back/buttock	13 (20)	17 (25)	24 (36)	34 (52)	38 (58)	34 (50)
Neck	9 (14)	10 (15)	11 (16)	10 (15)	15 (23)	15 (22)
Limb	41 (63)	52 (76)	41 (61)	30 (45)	25 (38)	32 (47)
Other†	12 (18)	12 (18)	1 (1)	0 (0)	5 (8)	3 (4)
Median SF-36 score (IQR)						
Physical functioning	55.0 (35.0–70.0)	45.0 (22.5–70.0)	55.0 (35.0–65.0)	52.5 (35.0–75.0)	45.0 (20.0–70.0)	55.0 (40.0–71.1)
Role functioning/physical	0.0 (0.0–25.0)	0.0 (0.0–50.0)	0.0 (0.0–50.0)	0.0 (0.0–50.0)	0.0 (0.0–50.0)	18.8 (0.0–25.0)
Role functioning/emotional	100.0 (0.0–100.0)	33.3 (0.0–100.0)	100.0 (33.3–100.0)	100.0 (33.3–100.0)	100.0 (33.3–100.0)	83.3 (33.3–100.0)
Energy/fatigue	45.0 (25.0–60.0)	40.0 (25.0–55.0)	45.0 (30.0–60.0)	45.0 (35.0–55.0)	45.0 (30.0–60.0)	45.0 (30.0–55.0)
Emotional well-being	76.0 (56.0–88.0)	68.0 (54.0–82.0)	72.0 (60.0–88.0)	76.0 (56.0–88.0)	72.0 (56.0–88.0)	72.0 (56.0–88.0)
Social functioning	50.0 (37.5–75.0)	50.0 (25.0–75.0)	62.5 (37.5–75.0)	50.0 (37.5–75.0)	62.5 (50.0–75.0)	50.0 (37.5–75.0)
Pain	32.5 (22.5–45.0)	22.5 (22.4–45.0)	32.5 (22.5–45.0)	33.8 (22.5–45.0)	22.5 (22.5–45.0)	32.5 (22.5–45.0)
General health	55.0 (35.0–75.0)	50.0 (30.0–70.0)	60.0 (40.0–75.0)	57.5 (40.0–75.0)	55.0 (40.0–70.0)	60.0 (42.5–75.0)
Coexisting psychiatric condition, *n (%)*						
None	51 (78)	53 (78)	47 (70)	46 (70)	47 (72)	50 (74)
Depression	10 (15)	12 (18)	10 (15)	13 (20)	9 (14)	11 (16)
Anxiety	9 (14)	8 (12)	9 (13)	11 (17)	9 (14)	9 (13)
PTSD	3 (5)	5 (7)	0 (0)	1 (2)	1 (2)	0 (0)
Substance abuse	3 (5)	1 (1)	9 (13)	11 (17)	9 (14)	8 (12)
Other‡	1 (2)	3 (4)	4 (6)	4 (6)	3 (5)	3 (4)
Multiple	3 (5)	2 (3)	4 (6)	6 (9)	5 (8)	3 (4)

BMI = body mass index; IQR = interquartile range; MEQ = morphine equivalents; PTSD = posttraumatic stress disorder; SF-36 = Short Form-36 Health Survey.
* May include more than 1 category.
† Includes abdomen, groin, chest, and head.
‡ Includes bipolar disorder, attention deficit–hyperactivity disorder, panic attacks, and autism.

Randomization and Interventions

We intended to perform our analyses by pain classification groups, upon which our power calculations were based, as well as in the pooled group of all patients. Equal numbers of participants were allocated to 3 subgroups on the basis of pain type: neuropathic, nociceptive, or mixed. A research pharmacist randomly assigned patients in each subgroup to receive either a compounded topical preparation or an identical odorless placebo cream by using a 1:1 ratio via a computer-generated randomization table in blocks of 2, 4, and 6 (in random order). The randomization sequence and assignments were concealed in separate, locked offices. Participants were enrolled by investigator physicians and the chief research nurse.

Pain was categorized mainly by the pain medicine board–certified treating physician, who considered historical and examination findings, imaging, and results from other relevant diagnostic tests. This designation was confirmed by the research nurse, who consulted the senior investigator (S.P.C.) for confirmation or adjudication in fewer than 5% of cases. Although 2 instruments that facilitate pain classification—painDETECT and the self-report version of the Leeds Assessment

All Patients	
Placebo (*n* = 197)	**Drug (*n* = 202)**
51.0 (39.0–64.0)	50.0 (38.0–64.0)
100 (51)	103 (51)
28 (14)	28 (14)
65 (33)	67 (33)
110 (56)	119 (59)
59 (30)	55 (27)
17 (9)	13 (6)
89 (45)	109 (54)
17 (9)	12 (6)
11 (6)	11 (5)
10 (5)	8 (4)
33 (17)	20 (10)
28 (14)	32 (16)
9 (5)	10 (5)
4.0 (1.0–10.0)	4.0 (1.5–8.0)
5.5 (1.4)	5.5 (1.3)
7.9 (1.6)	7.7 (1.6)
37 (19)	50 (25)
153 (78)	164 (81)
37 (19)	28 (14)
7 (4)	10 (5)
75 (38)	85 (42)
35 (18)	35 (17)
107 (54)	114 (56)
18 (9)	16 (8)
50.0 (30.0–70.0)	50.0 (30.0–72.2)
0.0 (0.0–25.0)	0.0 (0.0–50.0)
100.0 (33.3–100.0)	66.7 (0.0–100.0)
45.0 (30.0–60.0)	45.0 (30.0–55.0)
72.0 (56.0–88.0)	72.0 (56.0–84.0)
62.5 (37.5–75.0)	50.0 (25.0–75.0)
32.5 (22.5–45.0)	32.5 (22.5–45.0)
55.0 (40.0–70.0)	55.0 (35.0–75.0)
145 (74)	149 (74)
29 (15)	36 (18)
27 (14)	28 (14)
4 (2)	6 (3)
21 (11)	20 (10)
8 (4)	10 (5)
12 (6)	11 (5)

of Neuropathic Symptoms and Signs pain scale—were used as needed to help in categorization, physician designation is considered the reference standard (20, 21).

Pain cream formulations were selected on the basis of accepted systemic indications for neuropathic and nociceptive pain (22). The concentrations of individual medications were based on previous trials that evaluated topical use, with all falling into the mid- to high (ketamine) range (11, 15, 23, 24). These combinations are used frequently in marketed compounded formulations (25). Participants with predominantly neuropathic pain received a cream containing 10% ketamine, 6% gabapentin, 0.2% clonidine, and 2% lidocaine. Patients with nociceptive pain received a cream with 10% ketoprofen, 2% baclofen, 2% cyclobenzaprine, and 2% lidocaine. Those considered to have a mixed pain disorder (such as axial pain with radiculopathy) received a cream containing 10% ketamine, 6% gabapentin, 3% diclofenac, 2% baclofen, 2% cyclobenzaprine, and 2% lidocaine. Creams were formulated by using a lipophilic-based carrier (Transdermal Pain Base [Medisca]) and placed through the compounding mill twice to decrease particle size, which enhances penetration. Before the study began, a sample of each cream was sent to an independent analytical laboratory, which measured the amount of degradation of each component at various time points. On the basis of the laboratory's assessment, and controlling for a 10% variance in any individual medication, the creams were given an expiration date of 2 months.

Creams were applied to the affected areas 3 times per day, with the amount dispensed determined by the size of the area. A set amount was dispensed by rotating the bottom of the container, with each full rotation generating a click; the larger the area, the greater the number of clicks (for example, 4 rotations were used for a 5 × 5-inch pain area). If a discrepancy arose between the pain generator and pain location, the cream typically was applied to both the purported symptom source and the site of manifestation (for example, the wrist and fingers for carpal tunnel syndrome). Treatment adherence was assessed at 1 and 3 months via structured questions (for example, "Over the course of the month, how many treatment sessions did you miss?"). Except for physical therapy, baseline medications, and exercise—which were allowed to continue if ongoing—no co-interventions were permitted.

Outcomes and Follow-Up

All data, including adverse events, were collected in person (or via telephone if necessary) by a trained, blinded investigator not involved in patient care. Baseline data included age; sex; obesity status; pain type; primary diagnosis; pain duration; pain location; presence or absence of allodynia; active duty status; inciting event; coexisting psychiatric disorders; stable use of analgesic medications, including opioids; Short Form-36 Health Survey (SF-36) score; and average and worst pain scores on a 0- to 10-point numerical rating scale during the preceding week. The SF-36 is a validated measure of 8 domains, including emotional health and physical function, with lower scores translating to greater disability (26). After treatment, participants were instructed to record their average and worst pain scores twice per day in a pain diary, which was used to calculate outcomes.

The first follow-up visit occurred 1 month after the start of treatment (window, 24 to 40 days). The primary outcome measure was average pain score on a 0- to 10-point numerical rating scale, reflecting pain in the preceding week on the basis of the arithmetic mean from the pain diary. Secondary outcome measures included mean worst pain score over the past week, sat-

isfaction with treatment on a 1- to 5-point Likert scale (1, very unsatisfied; 3, neither unsatisfied nor satisfied; 5, very satisfied) (27), SF-36 scores, adverse effects (rated as serious or nonserious), reduction in analgesic medication use (predefined as a >20% reduction in opioid use or complete cessation of nonopioid analgesics) (28), treatment adherence, and each participant's guess as to his or her treatment allocation. In addition to individual variables, a positive composite outcome was designated as a decrease in average pain of at least 2 points coupled with score above 3 on the 5-point satisfaction scale (29). The original protocol required a satisfaction score of at least 4 points for a positive outcome, but this criterion was amended to greater than 3 points after it appeared that several participants circled 2 scores or marked the area between 2 numbers.

Participants with a positive 1-month categorical outcome had their final follow-up visit at 3 months (window, 75 to 110 days), at which time the same outcome data were recorded. Because of ethical concerns, participants with a negative 1-month outcome were unblinded and exited the study per protocol to receive nonstudy interventions.

Statistical Analysis

Our power analysis considered both the primary outcome of average pain score and the positive composite outcome, and provided adequate power within each pain classification group. Assuming a baseline average pain score of 6, a total of 60 participants per treatment group (120 per pain group; 360 overall) would provide 90% power to detect a pain reduction of 1.2 points, assuming an SD of 2 for reduction in pain and an alpha (2-sided) of 0.05. Sixty participants per treatment group would also provide 90% power to detect a 25% absolute difference (12% vs. 37%) in the positive composite outcome. Accounting for a 10% dropout rate, we elected to enroll a total of 399 patients, 133 for each pain category.

The primary analysis used an intention-to-treat approach in which patients were analyzed according to their original treatment assignment. For continuous data, we applied parametric and nonparametric tests, as indicated on the basis of results from the Shapiro–Wilk test, frequency histograms, and examination of Q–Q plots. For categorical data, we used a Fisher exact test. We compared changes from baseline in continuous outcomes by treatment group by using linear mixed-effects models with a random intercept and fixed effects for time, treatment, and time-by-treatment interaction. For binary outcomes, we calculated risk differences and 95% CIs in patients with complete data. A priori, we planned to examine the pain classifications separately and collectively. We conducted an exploratory prespecified subgroup analysis to examine outcomes by pain location. All analyses were performed in Stata, version 15.1 (StataCorp). Additional details of the statistical analysis plan are presented in the Supplement.

Role of the Funding Source

The funding sources paid for personnel and medications. They had no input in study design, execution, data analysis, interpretation, or decisions regarding manuscript submission.

RESULTS

Of the 399 patients randomly assigned and included in the intention-to-treat population, 396 received treatment and 390 completed the study protocol. Of the 399 participants, 202 were assigned to receive the study drug and 197 to receive placebo (Figure 1). Six patients in the neuropathic pain group and 3 in the mixed pain group either withdrew or were lost to follow-up. Baseline characteristics are shown in Table 1.

Primary Outcome

The change in pain score at 1 month did not differ between the drug and placebo groups for any type of

Table 2. Treatment Outcomes, by Pain Classification and for All Patients at 1 Month

Characteristic*	Neuropathic Pain			Nociceptive Pain		
	Drug (*n* = 68)	Placebo (*n* = 65)	Difference (95% CI)	Drug (*n* = 66)	Placebo (*n* = 67)	Difference (95% CI)
Primary outcome						
Change in average pain score from baseline (SD)	−1.4 (2.3)	−1.3 (1.5)	−0.1 (−0.8 to 0.5)	−1.4 (1.6)	−1.1 (1.6)	−0.3 (−0.9 to 0.2)
Secondary outcomes						
Positive outcome, *n (%)*†	20 (30)	17 (27)	4% (−12% to 19%)	23 (35)	19 (28)	6% (−9% to 22%)
Positive satisfaction, *n (%)*‡	23 (35)	20 (31)	4% (−13% to 20%)	30 (45)	26 (39)	7% (−10% to 23%)
Exploratory outcomes						
Change in worst pain score from baseline (SD)	−1.3 (2.1)	−1.4 (2.0)	0.1 (−0.6 to 0.8)	−1.3 (2.2)	−1.4 (1.9)	0.1 (−0.6 to 0.8)

* Results for average pain score and worst pain score are from the linear mixed-effects model. Negative differences for pain scores indicate greater reduction in pain with drug versus placebo. Differences for binary outcomes indicate risk difference. Missing data at 1 month include values for neuropathic pain for 2 patients in the drug group and 1 patient in the placebo group, mixed pain for 1 patient in the placebo group, and all patients for 2 patients in the drug group and 2 in the placebo group.
† ≥2-point decrease in average pain score and >3 on a 5-point Likert satisfaction scale.
‡ Classified as scores >3 on a 1–5-point Likert scale ranging from very unsatisfied to very satisfied with treatment results. "Satisfied" is defined as a score >3.

pain classification (−0.1 points [95% CI, −0.8 to 0.5 points] for neuropathic pain, −0.3 points [CI, −0.9 to 0.2 points] for nociceptive pain, and −0.3 points [CI, −0.9 to 0.2 points] for mixed pain) (Table 2 and Figure 2). Among all patients combined, the change in average pain scores also did not differ between the drug and placebo groups (−0.3 points [CI, −0.6 to 0.1 points] favoring drug). The lower 95% confidence bounds for the 1-month between-group differences were all 0.9 points or less and excluded clinically meaningful benefits with the compounded topical pain cream.

Secondary Outcomes

The SF-36 measures did not differ between the 2 study groups for any type of pain classification or for the cohort (Appendix Table 1, available at Annals.org). Similar rates of satisfaction and positive outcome were found between the active treatment and control groups at 1 month (43% vs. 38% for positive satisfaction and 36% vs. 28% for positive outcome, respectively; n = 395) (Table 2) and at 3 months for patients with a positive 1-month outcome who remained in the study (94% vs. 90% for positive satisfaction [n = 120] and 81% vs. 75% for positive outcome [n = 121], respectively).

Exploratory Analyses

Worst pain score and medication reduction at 1 and 3 months did not differ between the drug and placebo groups for any type of pain classification or for all patients. At 3 months, no difference in average pain score was observed between the drug and placebo groups for the entire cohort or any pain classification (Appendix Table 2, available at Annals.org). Examination of treatment outcomes by 4 different pain locations revealed no differences between drug and placebo with regard to pain scores, SF-36 measures, medication reduction, satisfaction scores, or positive outcome at 1 month (Appendix Table 3, available at Annals.org).

Effectiveness of Blinding and Adherence

At 1 month, 58 of 198 participants (29%) randomly assigned to the active treatment group guessed that they received the drug and 72 of 195 (37%) assigned to the control group guessed that they received placebo. At 1 month (n = 393), adherence was reported as full (>90%) in 77%, partial (50% to 89%) in 16%, and poor (<50%) in 7% of participants. At 3 months (n = 120), adherence was reported as full in 77%, partial in 18%, and poor in 5% of participants.

Adverse Events

Side effects were similar at 1 and 3 months for all pain classifications (Table 3), and no serious adverse events occurred. Among all patients, a higher proportion in the active treatment than the control group reported irritation at 1 month (7% vs. 2%). The most commonly reported side effect in the drug group was skin irritation, followed by rash and redness.

DISCUSSION

We found no evidence of effectiveness in 3 compounded topical pain creams specially formulated to treat neuropathic, nociceptive, and mixed localized chronic pain. Although participants in both treatment and control groups had improvement in their pain throughout the study, no significant differences were observed in pain scores, functional improvement, or satisfaction in the cohort or any subgroup. In addition, although a slightly greater percentage of persons in the entire cohort had a positive 1-month outcome, no significant differences were observed in any subgroup, and the proportion of patients who had a positive 3-month outcome was very small.

Our study is consistent with previous studies showing a lack of efficacy for most topical pain creams. Although some randomized trials suggest utility for capsaicin (vanilloid 1 agonist), lidocaine (Na^+ channel blocker), and NSAIDs for knee osteoarthritis (cyclooxy-

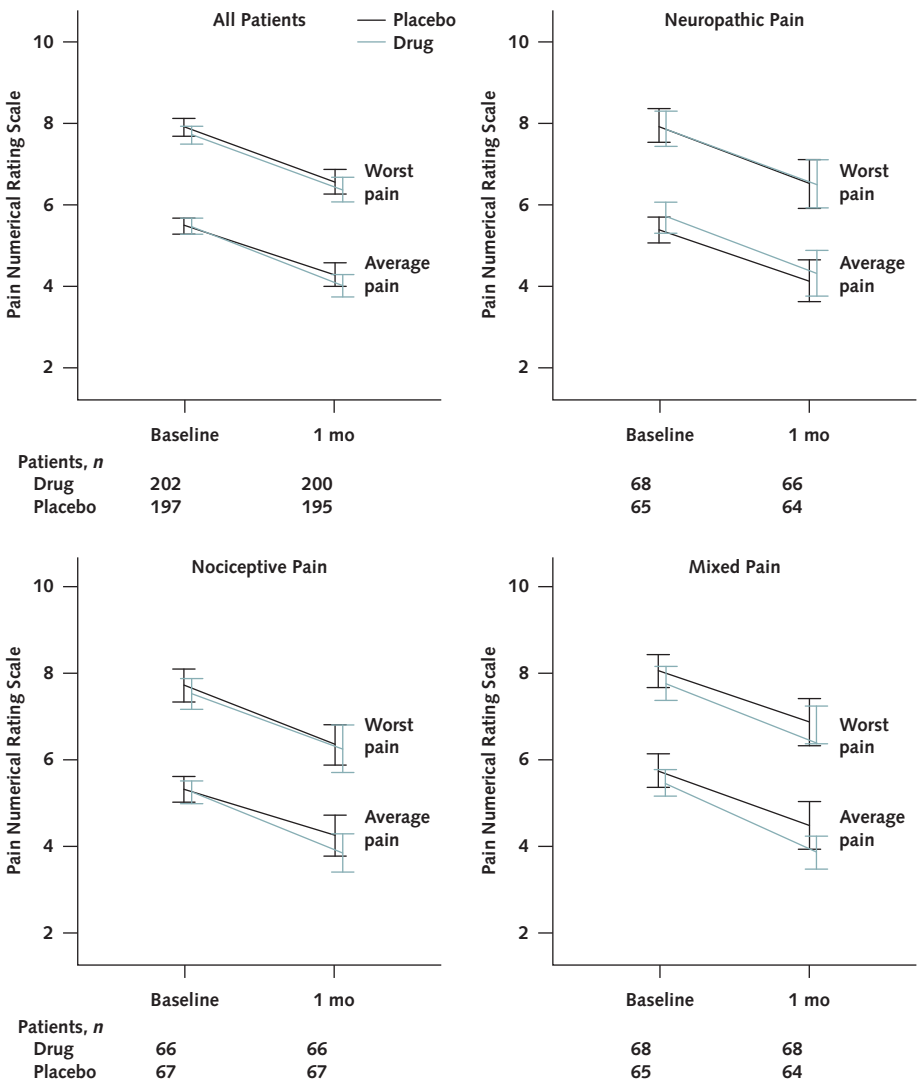
Mixed Pain			All Patients		
Drug (n = 68)	Placebo (n = 65)	Difference (95% CI)	Drug (n = 202)	Placebo (n = 197)	Difference (95% CI)
−1.6 (1.6)	−1.3 (1.6)	−0.3 (−0.9 to 0.2)	−1.5 (1.8)	−1.2 (1.6)	−0.3 (−0.6 to 0.1)
29 (43)	18 (28)	13% (−3% to 29%)	72 (36)	54 (28)	8% (−1% to 17%)
32 (47)	28 (44)	3% (−14% to 20%)	85 (43)	74 (38)	5% (−5% to 14%)
−1.4 (2.0)	−1.2 (1.9)	−0.2 (−0.9 to 0.5)	−1.3 (2.1)	−1.3 (1.9)	0.0 (−0.4 to 0.4)

genase inhibitor), we could not demonstrate a benefit in our population. Topical capsaicin is approved by the U.S. Food and Drug Administration (FDA) as an over-the-counter preparation in low concentrations for muscle, joint, and neuropathic pain and via prescription as a high-concentration, single-application patch for postherpetic neuralgia. In contrast, topical lidocaine is FDA approved only for postherpetic neuralgia, as a patch formulation applied for 12 hours in a 24-hour cycle; topical NSAIDs, which are available in both patch and cream form, are approved only for osteoarthritis of joints amenable to topical treatment, which is a nociceptive pain state. A recent Cochrane review on topical NSAIDs found efficacy only for knee osteoarthritis (30), which affected a small percentage of our patients.

Whereas topical lidocaine and NSAIDs may afford benefit because the predominance of their binding sites are in the peripheral nervous system, most compounds contained in the applied skin creams are ligands for receptors in the central nervous system. Because of their chemical properties, or the lack of an effective delivery system for small lipophilic compounds that may be candidates for transdermal delivery (such as ketamine), these agents are unlikely to reach their sites of action via topical application. With regard to clonidine, although α_2-receptors are situated in both the central and peripheral nervous systems—and a small uncontrolled study in persons with complex regional pain syndrome found that local application alleviated hyperalgesia—most of its analgesic properties derive from its effects on receptors in the spinal cord (31, 32).

Considering the analgesic effects of lidocaine and NSAIDs, why did so few of our study participants benefit from receiving these drugs in combination with other medications with systemic antinociceptive ef-

Figure 2. Pain outcomes over the study period, stratified by treatment group.



Pain intensity during the past week is scored on the numerical rating scale for worst pain and average pain at baseline and 1 month for drug (green) versus placebo (black). Trend lines connect mean values, whereas bars with whiskers represent 95% CIs for unadjusted means at each interval.

Table 3. Side Effects, by Pain Classification and for All Patients, Drug Versus Placebo

Characteristic	At 1 month, *n* (%)							
	Neuropathic Pain		Nociceptive Pain		Mixed Pain		All Patients	
	Placebo (*n* = 64)	Drug (*n* = 66)	Placebo (*n* = 67)	Drug (*n* = 66)	Placebo (*n* = 64)	Drug (*n* = 68)	Placebo (*n* = 195)	Drug (*n* = 200)
Any side effects	5 (8)	8 (12)	9 (13)	9 (14)	10 (16)	18 (26)	24 (12)	35 (18)
Redness	0 (0)	1 (2)	3 (4)	1 (2)	2 (3)	5 (7)	5 (3)	7 (4)
Itching	2 (3)	0 (0)	3 (4)	2 (3)	2 (3)	3 (4)	7 (4)	5 (3)
Irritation	0 (0)	3 (5)	2 (3)	5 (8)	1 (2)	6 (9)	3 (2)	14 (7)
Allergic response	1 (2)	0 (0)	0 (0)	1 (2)	1 (2)	0 (0)	2 (1)	1 (1)
Headache	0 (0)	1 (2)	1 (1)	0 (0)	2 (3)	2 (3)	3 (2)	3 (2)
Dizziness	0 (0)	0 (0)	0 (0)	0 (0)	2 (3)	3 (4)	2 (1)	3 (2)
Rash	1 (2)	4 (6)	2 (3)	3 (5)	2 (3)	3 (4)	5 (3)	10 (5)
Other*	1 (2)	0 (0)	0 (0)	3 (5)	5 (8)	8 (12)	6 (3)	11 (6)
	At 3 months, *n* (%)							
	Placebo (*n* = 15)	Drug (*n* = 17)	Placebo (*n* = 18)	Drug (*n* = 23)	Placebo (*n* = 18)	Drug (*n* = 27)	Placebo (*n* = 51)	Drug (*n* = 67)
Any side effects	1 (7)	1 (6)	2 (11)	2 (9)	1 (6)	2 (7)	4 (8)	5 (7)
Redness	0 (0)	0 (0)	0 (0)	1 (4)	0 (0)	1 (4)	0 (0)	2 (3)
Itching	1 (7)	0 (0)	1 (6)	0 (0)	1 (6)	1 (4)	3 (6)	1 (1)
Irritation	0 (0)	0 (0)	1 (6)	1 (4)	0 (0)	1 (4)	1 (2)	2 (3)
Allergic response	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Headache	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Dizziness	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Rash	0 (0)	1 (6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)
Other†	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (4)	0 (0)	1 (1)

* Includes skin peeling (neuropathic pain–placebo group); patchy dry skin, greasy feeling, and "not described" (nociceptive pain–drug group); tachycardia, lightening of skin and diminishing of age spots, insomnia, constipation, metallic taste (mixed pain–placebo group); and burning sensation, blisters, irritable mood, skin peeling, cold sensation in feet (2 patients), upset stomach and euphoria, itchy throat (mixed pain–drug group).
† Includes weight gain and dry skin (mixed pain–drug group).

fects? Compounded pain creams typically cost thousands of dollars, which is justified by the conceptual appeal of rational polypharmacy, which has been shown to be superior to monotherapy for chronic pain (33). Given the concerns surrounding use of medications that may affect cognition and psychomotor ability in service members, compounding creams are an attractive treatment option. Because of their young age, service members, especially those with posttraumatic stress, are at high risk for opioid misuse, and opioids may render a service member nondeployable or, in some cases, be grounds for terminating service. These concerns are postulated to have contributed to the high rate of compounded pain cream use in the Tricare population. Among Medicare beneficiaries, such issues as drug–drug interactions and the vulnerability of elderly persons to side effects may have led to high rates of use.

Administered as stand-alone agents, lidocaine and NSAIDs may alleviate pain, although the effect size is small and the number needed to treat is large (34, 35). Without penetration enhancers, topical medications diffuse less than 5 mm into the dermis, so it is not surprising that the conditions most amenable to skin administration are knee osteoarthritis for NSAIDs and evoked neuropathic pain (such as postherpetic neuralgia) for lidocaine. Paradoxically, administering these medications as a small component with other inert substances may dilute their effect.

We found that specially formulated compounded pain creams provided little benefit in our study participants, more than 40% of whom were active-duty personnel. Multivariable analysis found a small effect for active cream in the entire cohort, with differences among the subgroups falling short of statistical significance. Overall, the response rate was lower than that afforded by stand-alone creams shown to be effective for specific conditions, such as NSAIDs and lidocaine (30, 36). Considering the increased costs of using a non–FDA-approved and regulated compounded cream rather than a single agent, we caution against routine use of compounded creams for chronic pain.

Our study had several limitations. First, conventional treatments had failed in some of our patients before they enrolled in the study, increasing the likelihood that subsequent therapy would not be effective. In a study designed to determine efficacy, stringent selection criteria increase the chance of detecting a small treatment effect, and patients with long-standing pain or a coexisting psychopathologic condition would probably be excluded from an industry-sponsored trial. Second, although we included some analgesics shown to provide benefit via topical administration, we did not include capsaicin, which is FDA-approved for both neu-

ropathic and nociceptive pain, or amitriptyline, which is not approved for chronic pain and has not been shown to be effective topically (16). Capsaicin is not usually included in compounded pain creams because its application causes discomfort, so its use would undermine blinding. Therefore, the generalizability of our results to studies using these compounds, as well as other compounded pain creams containing different compositions, is limited. Third, our relatively young military population may have been less likely to have some of the pain conditions shown in clinical trials to be alleviated by topical creams, such as knee osteoarthritis (NSAIDs) and postherpetic neuralgia (lidocaine), which are more common in elderly persons. Fourth, although our initial protocol stated that adherence would be measured by weighing creams and estimating missed doses, these steps were not possible because of the variation in volumes used due to application of different amounts over different surface areas. Fifth, the conditions that affected our population were heterogenous, which enhances generalizability and is consistent with study indications and marketing; however, the failure to target specific diagnoses leaves open the possibility that some conditions might respond to compounded creams. Other limitations included the short follow-up and questionable reproducibility of pain categorization.

In summary, this randomized controlled trial failed to demonstrate meaningful benefit for 3 specially formulated compounded pain creams versus placebo or approved topical pain creams for various pain conditions. Future studies should seek to determine whether targeting specific types of pain or adding other agents (such as dimethyl sulfoxide) would lead to better results.

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Data Sharing Statement: The following data will be made available upon publication until 5 years after publication: complete deidentified patient data set (contact Steven P. Cohen; e-mail, scohen40@jhmi.edu). The following supporting documents will be made available upon publication until 5 years after publication: analytic/statistical code and informed consent forms (contact Steven P. Cohen; e-mail, scohen40@jhmi.edu). These data will be made available to anyone requesting it for any purpose with investigator support.

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Appendix Table 1. Treatment Outcomes, by Pain Classification and for All Patients, at 1 Month

Characteristic*	Neuropathic Pain			Nociceptive Pain			Mixed Pain			All Patients		
	Drug (*n* = 68)	Placebo (*n* = 65)	Difference (95% CI)	Drug (*n* = 66)	Placebo (*n* = 67)	Difference (95% CI)	Drug (*n* = 68)	Placebo (*n* = 65)	Difference (95% CI)	Drug (*n* = 202)	Placebo (*n* = 197)	Difference (95% CI)
Secondary outcomes												
Change in SF-36 score from baseline (SD)												
Physical functioning	0.1 (18.9)	2.2 (20.7)	−2.0 (−8.8 to 4.8)	6.3 (18.1)	4.5 (19.4)	1.8 (−4.5 to 8.2)	4.7 (15.4)	4.4 (12.9)	0.3 (−4.6 to 5.1)	3.7 (17.6)	3.7 (18.0)	0.1 (−3.4 to 3.6)
Role functioning/physical	9.8 (44.2)	14.1 (36.2)	−4.3 (−18.1 to 9.4)	10.2 (34.8)	14.6 (34.9)	−4.3 (−16.1 to 7.4)	11.6 (38.0)	9.1 (41.0)	2.5 (−10.9 to 15.9)	10.5 (38.9)	12.6 (37.2)	−2.1 (−9.6 to 5.4)
Role functioning/emotional	16.7 (43.6)	4.7 (38.4)	11.1 (−3.0 to 25.2)	−2.0 (33.0)	−2.0 (29.5)	0.0 (−10.6 to 10.5)	6.4 (29.5)	1.6 (33.0)	4.9 (−5.7 to 15.6)	6.9 (36.4)	1.4 (33.7)	5.4 (−1.5 to 12.3)
Energy/fatigue	3.4 (14.9)	2.7 (17.1)	0.9 (−4.6 to 6.4)	3.0 (16.7)	−0.2 (14.0)	3.0 (−2.2 to 8.2)	3.8 (16.7)	3.3 (15.3)	0.4 (−5.0 to 5.9)	3.4 (16.1)	1.9 (15.5)	1.5 (−1.6 to 4.6)
Emotional well-being	5.2 (13.3)	1.6 (14.1)	3.8 (−0.9 to 8.5)	2.5 (11.2)	−0.4 (11.0)	2.8 (−1.0 to 6.5)	2.3 (11.7)	3.0 (12.8)	−0.7 (−4.9 to 3.5)	3.3 (12.1)	1.4 (12.7)	2.0 (−0.5 to 4.4)
Social functioning	10.2 (22.9)	5.5 (16.0)	4.8 (−1.9 to 11.6)	3.8 (19.1)	5.4 (15.4)	−1.6 (−7.5 to 4.2)	7.7 (20.1)	3.6 (17.3)	4.1 (−2.3 to 10.5)	7.2 (20.8)	4.8 (16.2)	2.4 (−1.3 to 6.1)
Pain	11.9 (20.5)	9.3 (15.2)	2.7 (−3.5 to 8.9)	8.1 (16.9)	8.4 (16.2)	−0.3 (−5.9 to 5.3)	14.4 (19.6)	8.4 (15.9)	5.8 (−0.3 to 11.9)	11.5 (19.1)	8.7 (15.7)	2.8 (−0.7 to 6.2)
General health	−0.3 (13.4)	0.2 (12.4)	−0.4 (−4.8 to 4.1)	−0.5 (12.7)	−4.0 (11.7)	3.4 (−0.7 to 7.5)	−1.0 (14.1)	1.2 (13.9)	−2.1 (−6.9 to 2.6)	−0.6 (13.3)	−0.9 (12.8)	0.4 (−2.2 to 2.9)
Exploratory outcomes												
Medication reduction, *n (%)*†												
No	45 (68)	41 (64)	−12% (−28% to 4%)	35 (53)	44 (66)	5% (−12% to 22%)	49 (72)	48 (75)	6% (−9% to 22%)	129 (65)	133 (68)	−2% (−11% to 7%)
Yes	11 (17)	19 (30)	–	17 (26)	17 (25)	–	14 (21)	12 (19)	–	42 (21)	48 (25)	–
Not applicable	10 (15)	4 (6)	–	14 (21)	6 (9)	–	5 (7)	4 (6)	–	29 (15)	14 (7)	–
30% reduction in pain from baseline, *n (%)*	25 (38)	23 (36)	2% (−15% to 19%)	29 (44)	26 (39)	5% (−12% to 22%)	34 (50)	19 (30)	20% (4% to 37%)	88 (44)	68 (35)	9% (−0.4% to 19%)

SF-36 = Short Form-36 Health Survey.

* Results for SF-36 values are from the linear mixed–effects model. Positive differences for SF-36 values indicate greater improvement in quality of life with drug versus placebo. Differences for binary outcomes indicate risk difference. Missing data at 1 month include values for neuropathic pain for 2 patients in the drug group and 1 patient in the placebo group, for mixed pain for 1 patient in the placebo group, and for all patients for 2 patients in the drug group and 2 in the placebo group. In addition, missing values at 1 month include SF-36 values for 2 patients in the drug group for neuropathic pain and all patients, 1 patient in the placebo group for mixed pain and all patients, and 1 additional patient for energy/fatigue and emotional well-being in the drug group for nociceptive pain and all patients.

† Defined as cessation of nonopioid analgesics or >20% decrease in opioid use.

Appendix Table 2. Three-Month Treatment Outcomes, by Pain Classification, for Patients With a Positive 1-Month Outcome*

Characteristic†	Neuropathic Pain			Nociceptive Pain			Mixed Pain			All Patients		
	Placebo (*n* = 16)	Drug (*n* = 18)	Difference (95% CI)	Placebo (*n* = 19)	Drug (*n* = 23)	Difference (95% CI)	Placebo (*n* = 18)	Drug (*n* = 27)	Difference (95% CI)	Placebo (*n* = 53)	Drug (*n* = 68)	Difference (95% CI)
Primary outcome												
Change in average pain score from baseline (SD)	−2.7 (1.4)	−2.8 (2.1)	0.0 (−1.0 to 1.0)	−1.8 (2.1)	−2.8 (2.2)	−0.9 (−1.9 to 0.0)	−2.5 (2.2)	−2.9 (1.6)	−0.3 (−1.2 to 0.6)	−2.3 (2.0)	−2.9 (1.9)	−0.5 (−1.0 to 0.1)
Secondary outcomes												
Positive outcome, *n (%)*‡	13 (81)	14 (78)	−0.1 (−0.5 to 0.4)	13 (68)	17 (74)	0.1 (−0.3 to 0.4)	14 (78)	24 (89)	0.2 (−0.2 to 0.6)	40 (75)	55 (81)	0.1 (−0.1 to 0.3)
Positive satisfaction, *n (%)*§	14 (88)	15 (83)	−0.1 (−0.5 to 0.4)	17 (94)	22 (96)	0.1 (−0.6 to 0.8)	16 (89)	27 (100)	0.6 (0.5 to 0.8)	47 (90)	64 (94)	0.2 (−0.1 to 0.5)
Change in SF-36 score from baseline (SD)												
Physical functioning	7.6 (26.5)	11.5 (13.4)	7.7 (−5.1 to 20.5)	17.9 (28.2)	12.2 (18.3)	−7.0 (−19.4 to 5.3)	10.8 (22.2)	12.9 (20.7)	1.9 (−9.9 to 13.7)	12.4 (25.7)	12.3 (18.0)	0.9 (−6.3 to 8.1)
Role functioning/physical	25.0 (38.7)	22.1 (47.5)	5.5 (−19.4 to 30.3)	35.5 (48.1)	17.4 (39.5)	−22.3 (−44.0 to −0.6)	19.4 (45.8)	32.7 (41.8)	12.2 (−9.6 to 33.9)	26.9 (44.4)	24.6 (42.5)	−2.0 (−15.1 to 11.1)
Role functioning/emotional	20.8 (31.9)	25.5 (43.3)	9.2 (−14.3 to 32.8)	10.5 (44.5)	4.3 (30.6)	−8.5 (−29.3 to 12.2)	7.4 (50.6)	7.7 (27.2)	8.5 (−13.3 to 30.2)	12.6 (43.0)	11.1 (33.8)	2.6 (−10.2 to 15.4)
Energy/fatigue	15.3 (24.7)	4.6 (17.8)	−7.0 (−20.0 to 6.0)	13.2 (13.5)	6.5 (23.6)	−9.3 (−20.2 to 1.7)	6.1 (17.4)	11.7 (19.9)	3.1 (−7.2 to 13.4)	11.4 (18.8)	8.1 (20.7)	−3.9 (−10.5 to 2.6)
Emotional well-being	6.3 (13.4)	4.4 (12.6)	−0.2 (−8.6 to 8.2)	1.3 (12.4)	6.4 (11.1)	4.1 (−2.7 to 10.9)	2.8 (13.2)	3.8 (15.1)	1.4 (−6.9 to 9.6)	3.3 (12.9)	4.9 (13.0)	1.7 (−2.8 to 6.3)
Social functioning	7.8 (21.3)	7.4 (24.2)	3.9 (−10.6 to 18.3)	13.2 (24.8)	12.5 (26.1)	−6.0 (−20.1 to 8.1)	6.3 (24.7)	19.2 (21.0)	11.9 (−0.6 to 24.4)	9.2 (23.5)	13.8 (23.8)	4.3 (−3.7 to 12.3)
Pain	13.9 (24.4)	18.5 (17.7)	6.7 (−5.4 to 18.8)	19.1 (13.0)	25.5 (26.1)	1.6 (−9.4 to 12.6)	18.3 (21.1)	26.5 (22.4)	5.1 (−5.6 to 15.9)	17.3 (19.6)	24.1 (22.6)	4.6 (−1.9 to 11.1)
General health	2.2 (11.3)	4.4 (16.0)	3.3 (−5.6 to 12.2)	0.0 (12.8)	6.1 (17.3)	3.5 (−5.2 to 12.2)	−2.8 (16.3)	2.3 (14.2)	3.9 (−4.7 to 12.5)	−0.3 (13.6)	4.2 (15.6)	3.9 (−1.2 to 9.0)
Exploratory outcomes												
Change in worst pain score from baseline (SD)	−3.1 (2.8)	−3.0 (1.9)	0.2 (−1.1 to 1.4)	−2.3 (2.5)	−3.4 (2.7)	−1.0 (−2.2 to 0.1)	−2.6 (1.8)	−3.4 (2.1)	−0.6 (−1.6 to 0.4)	−2.6 (2.4)	−3.3 (2.3)	−0.5 (−1.2 to 0.1)
Medication reduction, *n (%)*‖												
No	7 (44)	8 (44)	0.1 (−0.3 to 0.4)	11 (61)	12 (52)	0.1 (−0.2 to 0.4)	11 (61)	13 (48)	0.2 (−0.1 to 0.5)	29 (56)	33 (49)	0.1 (−0.1 to 0.3)
Yes	5 (31)	7 (39)	–	5 (28)	8 (35)	–	4 (22)	10 (37)	–	14 (27)	25 (37)	–
Not applicable	4 (25)	3 (17)	–	2 (11)	3 (13)	–	3 (17)	4 (15)	–	9 (17)	10 (15)	–
30% reduction in pain from baseline, *n (%)*	13 (81)	14 (78)	−0.1 (−0.5 to 0.4)	12 (63)	16 (70)	0.1 (−0.2 to 0.4)	13 (72)	22 (81)	0.1 (−0.2 to 0.5)	38 (72)	52 (76)	0.1 (−0.1 to 0.3)

SF-36 = Short Form-36 Health Survey.

* Only patients with a positive 1-month outcome remained blinded and were followed through 3 months.

† Negative differences for pain scores indicate greater reduction in pain with drug versus placebo. Positive differences for SF-36 values indicate greater improvement in quality of life with drug versus placebo. Differences for binary outcomes indicate risk difference. Missing values at 3 months include 1 medication reduction and satisfaction value from the placebo group for nociceptive pain and all patients, 1 SF-36 value from the drug group for neuropathic pain and mixed pain, and 2 SF-36 values from the drug group for all patients.

‡ ≥2-point decrease in average pain score and >3 on a 5-point Likert satisfaction scale.

§ Classified as scores >3 on a 1–5-point Likert scale ranging from very unsatisfied to very satisfied with treatment results. "Satisfied" is defined as a score >3.

‖ Defined as cessation of nonopioid analgesics or >20% decrease in opioid use.

Appendix Table 3. Treatment Outcomes, by Pain Location, at 1 Month

Characteristic*	Back/Buttocks			Neck			Limb			Other Location†		
	Placebo (*n* = 74)	Drug (*n* = 83)	Difference (95% CI)	Placebo (*n* = 34)	Drug (*n* = 35)	Difference (95% CI)	Placebo (*n* = 106)	Drug (*n* = 113)	Difference (95% CI)	Placebo (*n* = 18)	Drug (*n* = 15)	Difference (95% CI)
Primary outcome												
Change in average pain score from baseline (SD)	−1.0 (1.5)	−1.4 (1.8)	−0.4 (−0.9 to 0.2)	−0.9 (1.4)	−1.6 (2.0)	−0.7 (−1.5 to 0.1)	−1.4 (1.6)	−1.6 (1.9)	−0.2 (−0.7 to 0.3)	−0.7 (1.4)	−1.2 (2.7)	−0.5 (−1.9 to 0.8)
Secondary outcomes												
Positive outcome, *n (%)*‡	19 (26)	30 (36)	0.1 (−0.04 to 0.3)	8 (24)	10 (29)	0.1 (−0.2 to 0.3)	35 (33)	48 (42)	0.1 (−0.04 to 0.2)	1 (6)	2 (13)	0.2 (−0.3 to 0.8)
Positive satisfaction, *n (%)*§	27 (36)	37 (45)	0.1 (−0.1 to 0.2)	13 (38)	14 (40)	0.0 (−0.2 to 0.3)	46 (43)	52 (46)	0.0 (−0.1 to 0.2)	1 (6)	4 (27)	0.4 (0.01 to 0.8)
Change in SF-36 score from baseline (SD)												
Physical functioning	5.1 (15.1)	5.0 (21.7)	0.3 (−5.6 to 6.2)	5.0 (14.7)	5.9 (17.8)	0.5 (−7.1 to 8.1)	3.9 (18.3)	2.4 (14.8)	−1.6 (−6.0 to 2.8)	−6.7 (22.2)	3.3 (15.1)	10.8 (−2.1 to 23.7)
Role functioning/physical	11.0 (38.2)	11.4 (40.3)	0.5 (−11.7 to 12.8)	16.9 (25.2)	10.0 (46.3)	−7.1 (−24.5 to 10.2)	9.9 (38.5)	13.0 (40.8)	2.8 (−7.7 to 13.3)	15.3 (38.5)	11.7 (33.9)	−2.8 (−27.0 to 21.3)
Role functioning/emotional	−1.8 (35.1)	6.0 (37.9)	7.4 (−4.0 to 18.9)	2.9 (23.7)	8.6 (52.0)	6.1 (−12.8 to 24.9)	4.4 (35.7)	11.4 (39.1)	7.0 (−2.9 to 16.9)	−5.6 (17.1)	4.4 (11.7)	9.8 (−0.1 to 19.7)
Energy/fatigue	2.5 (14.8)	2.4 (16.4)	−0.1 (−5.1 to 4.8)	−2.1 (12.1)	5.9 (16.9)	7.5 (0.6 to 4.4)	2.7 (16.0)	3.9 (16.9)	1.2 (−3.2 to 5.5)	−2.5 (17.3)	6.7 (13.2)	9.6 (−0.7 to 19.9)
Emotional well-being	1.3 (12.8)	2.2 (13.4)	1.1 (−3.0 to 5.2)	1.3 (9.4)	5.1 (12.0)	3.7 (−1.4 to 8.7)	1.3 (10.6)	4.5 (12.2)	3.3 (0.2 to 6.3)	0.0 (21.6)	5.9 (7.8)	6.4 (−4.7 to 17.6)
Social functioning	2.4 (17.3)	6.2 (20.5)	3.9 (−2.0 to 9.9)	7.0 (16.3)	5.7 (19.3)	−1.4 (−9.8 to 6.9)	7.0 (15.2)	8.1 (22.0)	1.2 (−3.8 to 6.2)	−1.4 (14.8)	9.2 (18.6)	10.8 (−0.2 to 21.8)
Pain	8.0 (14.5)	14.2 (20.4)	6.3 (0.7 to 1.9)	11.8 (17.2)	16.6 (18.7)	4.6 (−3.7 to 12.9)	9.3 (16.1)	11.4 (19.4)	2.1 (−2.6 to 6.8)	3.5 (14.1)	10.3 (17.4)	7.4 (−3.0 to 17.8)
General health	0.1 (11.8)	−1.7 (13.3)	−1.7 (−5.7 to 2.2)	−0.1 (8.7)	0.6 (18.9)	0.7 (−6.1 to 7.6)	−0.4 (14.5)	−0.3 (12.9)	0.2 (−3.5 to 3.8)	−1.1 (13.9)	1.3 (8.3)	2.7 (−5.1 to 10.5)
Exploratory outcomes												
Change in worst pain score from baseline (SD)	−1.1 (1.7)	−1.3 (2.0)	−0.2 (−0.8 to 0.4)	−1.3 (1.6)	−1.6 (2.2)	−0.3 (−1.2 to 0.6)	−1.6 (2.0)	−1.5 (2.2)	0.1 (−0.5 to 0.7)	−0.4 (1.6)	−0.8 (2.1)	−0.4 (−1.6 to 0.8)
Medication reduction, *n (%)*‖												
No	46 (62)	47 (57)	0.0 (−0.2 to 0.2)	22 (65)	26 (74)	−0.3 (−0.5 to 0.01)	72 (68)	75 (66)	−0.1 (−0.2 to 0.1)	16 (89)	10 (67)	0.4 (−0.1 to 0.8)
Yes	21 (28)	23 (28)	–	11 (32)	4 (11)	–	24 (23)	20 (18)	–	1 (6)	3 (20)	–
Not applicable	7 (9)	13 (16)	–	1 (3)	5 (14)	–	10 (9)	18 (16)	–	1 (6)	2 (13)	–
30% reduction in pain from baseline, *n (%)*	20 (27)	34 (41)	0.2 (−0.01 to 0.3)	8 (24)	14 (40)	0.2 (−0.1 to 0.4)	46 (43)	55 (49)	0.1 (−0.1 to 0.2)	5 (28)	6 (40)	0.1 (−0.2 to 0.5)

SF-36 = Short Form-36 Health Survey.

* Negative differences for pain scores indicate greater reduction in pain with drug versus placebo. Positive differences for SF-36 values indicate greater improvement in quality of life with drug versus placebo. Differences for binary outcomes indicate risk difference. Missing values include medication reduction and satisfaction values from 1 patient in the placebo group for limb pain.

† Includes head, abdomen, groin, and chest.

‡ ≥2-point decrease in average pain score and >3 on a 5-point Likert satisfaction scale.

§ Classified as scores >3 on a 1–5-point Likert scale ranging from very unsatisfied to very satisfied with treatment results. "Satisfied" is defined as a score >3.

‖ Defined as cessation of nonopioid analgesics or >20% decrease in opioid use.