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Original Research Article

Opioid Use as a Predictor of Pain Outcomes in Iraq and Afghanistan Veterans with Chronic Pain: Analysis of a Randomized Controlled Trial

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Abstract

Objective. Our objectives were to: 1) assess the relationship between self-reported opioid use and baseline demographics, clinical characteristics and pain outcomes; and 2) examine whether baseline opioid use moderated the intervention effect on outcomes at 9 months. **Design**. We conducted a secondary analysis of data from the Evaluation of Stepped Care for Chronic Pain (ESCAPE) trial, which found stepped-care to be effective for chronic pain in military veterans. **Setting**. A post-deployment clinic and five general medicine clinics at a Veteran Affairs Medical Center. **Subjects**. In total 241 veterans with chronic musculoskeletal pain; 220 with complete data at 9 months. **Methods**. Examination of baseline relationships and multivariable linear regression to examine baseline opioid use as a moderator of pain-related outcomes including Roland Morris Disability Questionnaire (RMDQ), Brief Pain Inventory (BPI) Interference scale, and Graded Chronic Pain Scale (GCPS) at 9 months. **Results**. Veterans reporting baseline opioid use ($n = 80$) had significantly worse RMDQ (16.0 ± 4.9 vs. 13.4 ± 4.2, $P < .0001$), GCPS (68.7 ± 12.0 vs. 65.0 ± 14.4, $P = .049$), BPI Interference (6.2 ± 2.2 vs. 5.0 ± 2.1, $P < .0001$), and depression (PHQ-9 12.5 ± 6.2 vs. 10.6 ± 5.7, $P = .016$) compared to veterans not reporting baseline opioid use. Using multivariable modeling we found that baseline opioid use moderated the intervention effect on pain-related disability (RMDQ) at 9 months (interaction Beta $= -3.88$, $P = .0064$) but not pain intensity or interference. **Conclusions**. In a stepped-care trial for pain, patients reporting baseline opioid use had greater improvement in pain disability at 9 months compared to patients not reporting opioid use.

Key Words: Opioids; Primary Care; Chronic Pain; Treatment Outcome; Secondary Analysis

Introduction

Chronic pain is one of the most common symptoms causing adults to seek medical care, affecting 20% of the general population [1, 2]. The prevalence is even higher among combat veterans: pain was the most highly reported symptom in Persian Gulf War Veterans [3] and was reported in 40% to 50% of Veterans of Operations Enduring Freedom, Iraqi Freedom, and New Dawn (OEF/OIF/OND) [4, 5]. Chronic pain may prove even more disabling in OEF/OIF/OND Veterans than for veterans of previous eras due to the high combat intensity of Afghanistan and Iraq conflicts and an increased prevalence of comorbidities such as anxiety and depression [6].

Over the past few decades, opioid therapy has become a widespread treatment for chronic pain. At the prescribing zenith of 2010, opioid prescriptions outnumbered persons in many parts of the country, and this continues to be true in many counties across the United States [7, 8]. This widespread opioid prescribing has contributed to a rise in opioid-related deaths, with a 4.5-fold increase in opioid overdose death from 1999 to 2016 [9]. There were over 42,000 overdose deaths involving opioids in 2016, which amounts to an age-adjusted death rate of 13.3 per 100,000 [9]. This rate is even higher in veterans, with a reported rate of 21 deaths per 100,000 from opioid overdoses in 2016 [10]. Despite the widespread use of opioids to treat chronic pain, several studies have demonstrated nonsuperiority of opioids compared to alternative pain treatment strategies [11–13]. While alternative treatments for chronic pain, such as non-opioid analgesics and cognitive behavioral therapy, are gaining traction, there is a paucity of information addressing whether these treatments will differentially affect patients who have been on opioids for pain compared to patients who have not.

In this study, we analyzed data from a 9-month randomized clinical trial of a stepped-care intervention for veterans with chronic musculoskeletal pain to examine the relationship of baseline opioid use with baseline demographic and clinical characteristics and pain outcomes. Our specific objectives were to: 1) assess the relationship between self-reported opioid use and baseline demographics, clinical characteristics and pain outcomes in a pain treatment trial; and 2) examine whether baseline opioid use moderated the intervention effect on outcomes at 9 months. Compared to participants not reporting opioid use at baseline, we hypothesized those reporting opioid use would have worse baseline pain and mental health comorbidity but have similar pain outcomes in response to the stepped-care intervention at 9 months.

Methods

Data Source

We conducted a secondary analysis of the Evaluation of Stepped Care for Chronic Pain (ESCAPE) Trial. The ESCAPE Trial tested a stepped-care intervention versus usual care for veterans with chronic and disabling musculoskeletal pain. The Indiana University Institutional Review Board and Roudebush VA Medical Center Research Committee approved the study. The trial was monitored by an independent data and safety monitoring board and all enrolled patients gave written informed consent. All study procedures were followed in accordance with the ethical with the Helsinki Declaration.

Participants and Setting

ESCAPE participants were veterans of post-9/11 conflicts with chronic ($>$ 3 months) and disabling (Roland Morris Disability Scale score $\geq$ 7) musculoskeletal pain of the cervical or lumbar spine or extremities (shoulders, knees, and/or hips). Participants were enrolled from a post-deployment clinic and 5 VA primary care clinics with 9-month follow-up [14].

Intervention

The ESCAPE intervention, methods, and main results were previously described and published [14]. In brief, among veterans with chronic pain, the stepped-care intervention led to less pain related disability, pain severity and pain interference compared to usual care. The intervention involved 12 weeks of analgesic treatment and optimization according to an evidence-based algorithm [15] coupled with self-management strategies (step 1) followed by 12 weeks of cognitive behavioral therapy (step 2). All intervention aspects were delivered by nurse care managers (NCMs). The NCMs reviewed the care of intervention patients weekly with the physician-investigators and supervising psychologist. In addition, NCMs were scheduled to call participants biweekly for a total of 12 contacts during the trial period.

Step 1: NCMs obtained a detailed pain treatment history from patients at baseline, including the dosing and duration of previous analgesic trials. During step 1, NCMs followed a treatment algorithm developed by the ESCAPE investigators [15] to optimize analgesic therapy. This analgesic algorithm began with first-line, simple analgesics such as acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs), followed by topical analgesics, gabapentionids, tricyclic antidepressants, tramadol, short-acting opioids, and lastly long-term opioid analgesics. The NCMs conducted follow-up calls to assess changes in pain severity and interference, global improvement, patient desire for treatment change, and adherence. If bothersome side effects emerged, participants were switched to a different analgesic. Participants were also screened for anxiety and depression during contacts with the NCMs, and participants found to have major depression, post-traumatic stress disorder (PTSD) or severe anxiety were referred for mental health treatment. Ongoing care and treatment response was discussed at weekly case management meetings. Medication changes were prescribed by a physician-investigator and

dispensed through the medical center pharmacy, with oversight by a research pharmacist.

In addition to analgesic optimization, participants also received instruction in self-management strategies to treat pain. This program included education about the natural history of pain, common treatments for pain, and the importance of behavioral activation, including stretching, strengthening exercises, and resumption of normal activities as soon as possible. The program also included a "menu" of self-management pain treatments including relaxation techniques, goal setting, problem-solving, behavioral plans, and strategies to improve communication with health care providers.

Step 2: Upon completion of step 1, all participants proceeded immediately to step 2, where participants received a cognitive behavioral therapy (CBT) intervention. Six biweekly CBT sessions lasting approximately 45 minutes were delivered over the phone by the NCM, who received training and coaching from a pain psychologist. The CBT intervention focused on helping participants identify maladaptive thoughts, especially inaccurate interpretations of pain and its impact. Participants were then taught to assess the usefulness and accuracy of these thoughts and to substitute more adaptive cognitions. Between sessions, they were given homework to practice using these techniques.

Usual Care

Veterans randomized to the usual care arm were followed by their treating physician. They attended clinic visits at typical intervals, and received any specialty referrals or typical treatment adjustments—including pharmacologic and non-pharmacologic treatments for pain. In addition, they received educational handouts on musculoskeletal pain.

Opioid Use at Baseline

At study baseline, the NCMs asked participants about past and current analgesic use, including duration and dose. Participants were categorized as opioid users (n = 80) or nonusers (n = 161) based on their self-report of current use.

Measures

Outcome assessments were administered at baseline and 3, 6, and 9 months post-randomization. For this paper, only baseline and 9 month data were analyzed. The *primary study outcome* was pain-related disability as assessed by the 24-item Roland Morris Disability Questionnaire (RMDQ), which has been validated in patients with low back pain and other chronic pain conditions [16, 17]. Respondents select items that describe ways that their function has been altered "because of [their] back." Items are wide-ranging and include functional adaptations such as "I use a handrail," behavior changes such as "I stay at home" and emotional changes such as "I am more irritable." This scale is scored 0 to 24; higher scores represent more severe pain-related disability. Clinically important difference estimates for the RMDQ range 2–8 points depending on the methods used [18].

On the current analyses, two other pain outcomes were assessed: pain interference and pain severity. Pain interference was assessed by the Brief Pain Inventory (BPI) Interference Scale. The BPI Interference scale has seven items that rate how pain interferes with mood, physical activity, work, social activity, relations with others, sleep, and enjoyment of life (score 0 to 10). Higher scores indicate greater pain interference [19]. The seven items were averaged for an overall interference score and a 2-point change is considered clinically important [20]. Pain severity was measured by the seven-item, Graded Chronic Pain Scale (GCPS) [21], which includes three items assessing participants' pain intensity and four items assessing pain-related activity interference. GCPS item responses are transformed into a 0 to 100 score with higher scores representing more severe pain. Using a standard deviation estimation approach, a minimally-important difference for GCPS in this sample would be approximately 6–7 points [14, 22].

Statistical Analysis

To assess the relationship between self-reported opioid use at baseline and demographics, clinical characteristics and baseline pain outcome measures, we compared these measures in participants with self-reported opioid use to those who reported no use at baseline using χ^2 and t-tests for categorical and continuous variables, respectively. We presented the means and standard deviations for each continuous measure and frequency and percentages for each categorical measure. We used multivariable linear regression to examine baseline opioid use as a moderator of intervention effect on pain-related disability, pain interference, and pain severity at 9 months.

For each 9 month pain outcome, we included opioid use at baseline (Yes/No), study arm (stepped care vs usual care) and their interaction in the multivariable linear model. This model allowed us to directly examine the moderator effect based on the significance of the interaction [23]. We also entered relevant baseline characteristics (age, gender, race, number of medical diseases, baseline depression score, and number of pain regions, which was collapsed into a dichotomous variable of less than 3 sites vs 3 or greater sites). Baseline values for each outcome (RMDQ, BPI, and GCPS) were also controlled for and entered as covariates into each corresponding models. SAS (version 9.3) was used to conduct the analysis, and P values $< .05$ was deemed as statistically significant.

Results

Baseline Characteristics

The overall study sample (n = 241) had a mean age of 36.7 years (range, 21–73), was 88% male, 78% white and 13% black, and took a median (Q1, Q3) of 2 (1, 3) analgesics at baseline. As shown in Table 1, the opioid use group had significantly worse RMDQ scores (16.0 ± 4.9 vs 13.4 ± 4.2, $P < .0001$), GCPS scores (68.7 ± 12.0 vs. 65.0 ± 14.4, $P = .049$), and BPI-Interference scores (6.2 ± 2.1 vs. 5.0 ± 2.1, $P < .0001$) and depression (PHQ-9 12.5 ± 6.2 vs 10.6 ± 5.7, $P = 0.016$) compared to the non-opioid group. Other than a slightly higher education level in the non-opioid group (80% with greater than high school compared to 68% in opioid group, $P = .036$), the groups were comparable in all other baseline measures assessed. Our analytic sample for the multivariable linear regression included the 220 participants with available baseline and 9 month data. There were no statistically significant baseline differences between the analytic sample and those participants with 9 month data on age, sex, race, education, marital status, number of comorbidities, pain medications taken, or pain outcome scores. The only difference found was that patients missing 9 month data were significantly more likely to have PHQ-9 depression scores $\geq$ 10 at baseline (79% vs 55%, $P = .04$).

Opioid Use and Pain Disability at 9 Months

The results of the multivariable linear regression modeling are shown in Table 2; negative beta coefficient values indicate lower RMDQ scores (less disability) at 9 months. Only treatment intervention had a significant effect on pain disability (RMDQ) at 9 months. However, we found a significant interaction between baseline

Table 1 Baseline characteristics and outcome measures of patients with and without opioid use at baseline

Variable	Opioid Use (n = 80)	No Opioid Use (n = 161)	*P*-value
Age, mean (SD)	37 (9.1)	37 (10.4)	1.00
Men	72 (90%)	141 (88%)	.58
Race			.25
White	64 (80%)	121 (75%)	
Black	8 (10%)	23 (14%)	
Other	8 (10%)	17 (10%)	
Educational level			.036*
High school	25 (32%)	32 (20%)	
>High school	54 (68%)	128 (80%)	
Employment			.67
Employed	43 (54%)	103 (64%)	
Student	10 (13%)	20 (12%)	
Unemployed	27 (24%)	37 (24%)	
Income			.62
Comfortable	26 (33%)	62 (39%)	
Just Enough	39 (49%)	69 (43%)	
Not Enough	15 (19%)	30 (19%)	
Married	42 (53%)	89 (55%)	.42
Branch			.27
Army	56 (70%)	104 (65%)	
Navy	2 (3%)	16 (10%)	
Marine Corps	9 (11%)	13 (8%)	
Air Force	5 (6%)	8 (5%)	
National Guard	8 (10%)	20 (12%)	
Military Status			.93
Active	5 (6%)	9 (6%)	
Reserve	6 (7%)	11 (7%)	
National Guard	15 (18%)	36 (23%)	
Retired	22 (27%)	44 (28%)	
Discharged	32 (39%)	57 (36%)	
Deployment			.89
Iraq	61 (76%)	118 (74%)	
Afghanistan	6 (8%)	15 (9%)	
Other	12 (15%)	27 (17%)	
No. of medical diseases, mean (SD)	1.00 (0.89)	0.92 (1.03)	.55
PHQ-9 score, mean (SD)	12.49 (6.17)	10.55 (5.69)	0.016*
RMDQ, mean (SD)	16.04 (4.94)	13.42 (4.18)	<.0001*
GCPS, mean (SD)	68.7 (12.0)	65.0 (14.4)	.049*
BPI-interference, mean (SD)	6.16 (2.16)	4.98 (2.14)	<.0001*

SD=Standard Deviation.
*$P < .05$.

Table 2. Multivariable linear regression modeling the contribution of baseline measures to 9-month improvement in Roland Morris Disability Questionnaire

Variable	Beta	SE	T score	*P*-value
Baseline opioid use (no vs. yes)	1.44	0.99	1.45	.15
Intervention (control vs intervention)	4.27	1.15	3.71	.0003*
Baseline opioid use * intervention	−3.88	1.41	−2.76	.0064*
Gender (female)	1.38	1.01	1.37	.17
Race (black)	−0.79	1.01	−0.79	.43
Race (other)	0.22	1.18	0.19	.85
< 3 pain regions	−0.88	0.75	−1.17	.24
Age	0.03	0.04	0.73	.47
Medical diseases total	0.55	0.38	1.48	.14
Baseline PHQ-9 score	0.05	0.06	0.73	.47

SE=Standard Error.
*$P < .05$.

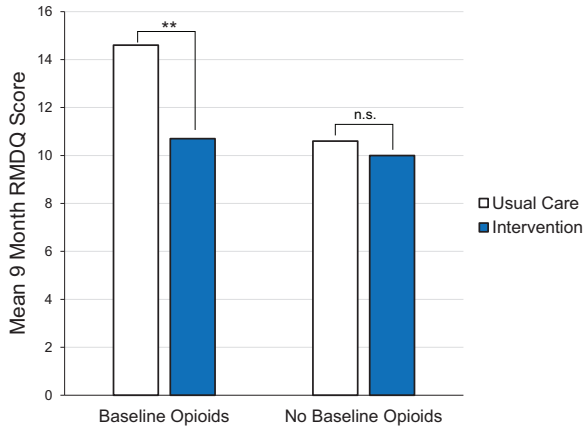

Figure 1. Mean 9 month Roland Morris Disability Questionnaire (RMDQ) scores by baseline opioid and intervention status. Significance value $P < .05$. **denotes $P < .01$, n.s. denotes not significant.

opioid use and study arm (interaction Beta = −3.88, $P = .0064$). Because of this interaction, in patients reporting being on opioids at baseline, the stepped-care intervention led to RMDQ scores at 9 months that were 4.27 points lower on average compared to patients receiving usual care. In contrast, for patients not taking opioids at baseline, pain disability at 9 months was not significantly different in patients who received the intervention compared to those who did not (lower by 0.40 points, $P = .63$). The interaction effect is demonstrated in Figure 1, which plots 9-month RMDQ scores by baseline opioid use and intervention status.

Opioid Use and Pain Severity at 9 Months

Table 3 shows the results of multivariable regression modelling to examine moderator effects of opioid use at baseline on pain severity (GCPS scores) at 9 months. Unlike with pain disability, we did not find an interaction between baseline opioid use and intervention for pain severity (GCPS interaction Beta = −2.0, $P = .65$). However, we did find that in addition to the stepped-care intervention, the number of pain regions at baseline had a significant effect on predicting 9 month pain severity. In veterans with less than three pain sites at baseline, pain severity (GCPS) at 9 months was lower by an average of 4.76 points more than for veterans who had three or greater pain sites at baseline ($P = .04$). Despite the lack of interaction between baseline opioid use and intervention in the multivariable model, the intervention effect on pain severity at 9 months trended lower in the baseline opioid use group, with a decrease of 8.34 points ($P = .024$) compared to 6.31 points ($P = .018$) in the non-opioid use group.

Opioid Use and Pain Interference at 9 Months

Results of the multivariable linear regression modeling found that the contribution of baseline characteristics in predicting pain interference (BPI-interference) at 9 months were similar to the pain severity model (Table 4). A significant interaction was not found between baseline opioid use and intervention (Beta = −0.85, $P = .15$). As with pain severity, the number of pain sites at baseline showed a strong effect on pain interference (BPI Interference) at 9 months. Veterans with fewer than 3 pain sites at baseline had 9 month BPI Interference scores that were on average 1.01 points lower than patients with three or greater pain sites at baseline ($P = .0015$). As with the pain severity (GCPS) model, the intervention effect on BPI Interference at 9 months trended lower in the opioid use group, with a decrease of 1.41 points ($P = .004$) compared to 0.56 points ($P = .11$) in the non-opioid group.

Discussion

Our study has several important findings. First, veterans reporting baseline opioid use had statistically worse

Table 3. Multivariable linear regression modeling the contribution of baseline measures to 9-month improvement in Graded Chronic Pain Scale

Variable	Estimate	SE	T score	*P*-value
Baseline opioid use (no vs. yes)	−5.20	3.15	−1.65	0.10
Intervention (control vs. intervention)	8.34	3.66	2.28	0.02*
Baseline opioid use * intervention	−2.03	4.53	−0.45	0.65
Gender (female)	0.16	3.23	0.05	0.96
Race (black)	−2.16	3.19	−0.68	0.50
Race (other)	5.79	3.75	1.54	0.12
< 3 pain regions	−4.76	2.33	−2.05	0.04*
Age	0.00	0.11	−0.02	0.99
Medical diseases total	2.22	1.19	1.86	0.06
Baseline PHQ-9 score	−0.12	0.19	−0.64	0.52

SE=Standard Error.
*$P < .05$.

Table 4. Multivariable linear regression modeling the contribution of baseline measures to 9 month improvement in BPI Interference Scores

Variable	Estimate	SE	T score	*P*-value
Baseline opioid use (no vs. yes)	0.09	0.43	0.21	.84
Intervention (control vs. intervention)	1.41	0.49	2.88	.0044*
Baseline opioid use * intervention	−0.85	0.60	−1.42	.16
Gender (female)	0.19	0.43	0.44	.66
Race (black)	−0.18	0.43	−0.43	.67
Race (other)	0.72	0.50	1.43	.15
<3 pain regions	−1.01	0.31	−3.22	.0015*
Age	0.00	0.02	0.06	0.95
Medical diseases total	0.26	0.16	1.62	0.11
Baseline PHQ-9 score	0.02	0.03	0.74	0.46

SE=Standard Error.
*$P < .05$.

baseline scores on all three pain measures and depression than veterans not reporting baseline opioid use. Second, the intervention effect on 9 month RMDQ scores (the primary outcome) in the ESCAPE trial was moderated by self-reported baseline opioid use. No such interaction was seen between baseline opioid use and GCPS or BPI Interference. Third, the number of pain sites at baseline was found to be significantly associated with 9 month GCPS and BPI Interference but not RMDQ.

A number of observational studies have found associations between long-term opioid use and worse pain outcomes including disability, pain severity, and psychological distress [24–29]. In a prior analysis of clinical trial data from the Stepped Care to Optimize Pain Care Effectiveness (SCOPE) trial, we found that baseline opioid use correlated with higher baseline pain scores, disability and probable major depression, but did not significantly affect the primary study outcome, as assessed by the BPI total score, which includes the seven items from the BPI Interference scale and the four items from the BPI Severity scale [30].

In the present study, we found a similar association between baseline opioid use and greater disability, pain severity, pain interference, and depression in OEF/OIF/OND Veterans enrolled in a clinical trial for chronic pain. While we did not assess the full 11-item BPI total score in the ESCAPE trial, analysis of the BPI Interference scale yielded similar results: baseline opioid use did not moderate pain interference at 9 months. We were surprised to find that our primary outcome of pain disability was moderated by baseline opioid use. While baseline pain disability (RMDQ) was higher in the group reporting opioid use, this was also the case for pain interference (BPI Interference) and pain severity (GCPS), where an interaction with baseline opioid use was not observed.

Although reported baseline opioid use was not independently associated with 9 month outcomes in the ESCAPE trial, the number of baseline pain sites was associated for two of the three primary pain outcomes. This finding underscores the importance of assessing baseline pain severity and number of pain sites involved, and that measures other than merely the intensity of pain or its interference in daily activities can be an important consideration. The differential interaction effect of baseline opioid use—that it moderates RMDQ but not GCPS or BPI Interference—highlights the differences in these scales and what constructs are assessed. A recent systematic review of patient reported outcome measures for pain found the RMDQ had high quality evidence demonstrating that it has poor unidimensionality, suggesting that it is measuring more than just pain-related disability [31]. In contrast, the BPI Interference scale was found to be unidimensional by moderate quality evidence, suggesting it truly is measuring only pain-related interference [31]. Furthermore, a recent retrospective study found that RMDQ scores did not change significantly when opioid dose was changed in patients on long-term opioid therapy for chronic pain [32].

Our finding that an intervention effect on pain disability as assessed by RMDQ scores depends on baseline opioid use further demonstrates that the RMDQ may be measuring a more complex phenomenon than simply the impact of pain on function. Why baseline opioid use would interact with disability score is not clear and would be a useful question for further research. A similar discordance between pain disability (RMDQ) and pain severity (GCPS)/pain interference (BPI-interference) was demonstrated by the finding that having 3 or more pain sites at baseline was associated with 9 month scores for pain severity and pain interference, but not the pain disability.

Our study has a number of strengths. Given that opioid overprescribing is a well-recognized problem, the question of whether current opioid use will affect response to alternative pain treatments is especially pertinent. Furthermore, the data analyzed in this study were collected during a longitudinal clinical trial with comprehensive data collection. In addition, we used multivariable regression analysis to control for several potential confounders.

Our study also has several limitations. First, this is a secondary analysis of a clinical trial that was not designed to answer these research questions. Opioid use had only been collected at baseline, preventing a more detailed assessment of this time-varying construct over the course of the trial. Hence, we can conclude that opioid use is a marker for a group of patients that responded better in terms of pain-related disability to a stepped-care intervention than patients who were not prescribed opioids, but we cannot comment on whether changes in opioid use during the intervention has any bearing on treatment outcomes. Second, the study was conducted exclusively in veterans who were predominantly men, therefore, findings may not generalize to different clinical

populations. Third, we did not review VA electronic medical records to confirm recent prescriptions consistent with participants' self-report of baseline opioid use.

Taken together, these findings suggest that current opioid use is not necessarily a poor prognostic sign regarding the efficacy of a stepped-care intervention involving non-opioid pain therapies for treating chronic pain. In fact, the impact of a stepped-care intervention on pain-related disability at 9 months in the ESCAPE clinical trial was dependent on baseline opioid use. Further research will be needed to replicate these findings in non-veteran samples and to further characterize the ways that opioid use may be influencing disability.

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