

ORIGINAL ARTICLE

Long-term improvements in sleep, pain, depression, and fatigue in older adults with comorbid osteoarthritis pain and insomnia

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Abstract

In a primary care population of 327 older adults (age 60+) with chronic osteoarthritis (OA) pain and insomnia, we examined the relationship between short-term improvement in sleep or pain and long-term sleep, pain, depression, and fatigue by secondary analyses of randomized controlled trial data. Study participants, regardless of trial arm, were classified as Sleep or Pain Improvers with $\geq 30\%$ baseline to 2-month reduction on the Insomnia Severity Index or the Brief Pain Inventory, respectively, or Sleep or Pain Non-Improvers. After controlling for trial arm and potential confounders, both Sleep and Pain Improvers showed significant ($p < .01$) sustained improvements across 12 months compared to respective Non-Improvers for the Insomnia Severity Index (ISI), Pittsburgh Sleep Quality Index, Brief Pain Inventory-short form (total, Interference, and Severity subscales), Patient Health Questionnaire, and Flinders Fatigue Scale. The effect sizes (Cohen's f^2) for the sustained benefits in both Sleep and Pain Improvers compared to their respective Non-Improvers for all variables were small (< 0.15) with the exception of medium effect size for sustained reduction in insomnia symptoms for the Sleep Improvers. We conclude that short-term sleep improvements in pain populations with comorbid insomnia precede benefits not only for long-term improvement in sleep but also for reduced pain over the long-term, along with associated improvements in depression and fatigue. Short-term improvements in pain appear to have similar long-term sequelae. Successfully improving sleep in pain populations with comorbid insomnia may have the additional benefits of improving both short- and long-term pain, depression, and fatigue.

Trial Registration: Osteoarthritis and Therapy for Sleep (OATS) NCT02946957: <https://clinicaltrials.gov/ct2/show/NCT02946957>.

Statement of Significance

Improving sleep of older adults with insomnia is associated with improvements in comorbid disorders such as pain, indicating that improving sleep in pain populations might also improve pain and other outcomes. Sleep or Pain Improvers (defined as $\geq 30\%$ baseline to 2-month reduction in insomnia symptoms or pain, respectively) showed significant sustained improvements at 12-months compared to respective Non-Improvers for sleep, pain, depression, and fatigue. Findings support an association between sleep and pain and demonstrate that short-term sleep improvement in older adults with osteoarthritis pain and insomnia precede long-term improvement in sleep, pain, depression, and fatigue. Successfully improving insomnia in pain populations may have the additional benefits of improving both short- and long-term pain, depression, and fatigue.

Key words: aging; cognitive-behavioral therapy; depression; fatigue; insomnia; osteoarthritis; pain; sleep

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Introduction

A growing literature suggests that improving the sleep of adults via cognitive behavioral therapy for insomnia (CBT-I) is associated with improvements in disorders comorbid with insomnia, including pain syndromes [1]. If so, improving sleep in pain populations might improve chronic pain and other outcomes common to insomnia and pain such as fatigue and depression [2]. Several trials evaluating CBT-I in pain populations have found improved sleep outcomes, but benefits of CBT-I for pain and associated outcomes have been inconsistent [3]. Moreover, the trials examining this question had significant limitations including small sample sizes, inadequate controls, recruitment of convenience samples, and short follow-ups, making it difficult to draw clear conclusions on the impact of improved sleep on comorbid pain, fatigue, and depression.

Previously we addressed this question through a secondary analysis of data from the “Lifestyles” study, a group-delivered randomized controlled trial (RCT) of CBT for insomnia and pain among older adults with comorbid osteoarthritis pain and insomnia [4, 5]. The Lifestyles trial provided an opportunity to assess the relationship between short-term improvement of sleep (baseline to 2-months [post-treatment]), regardless of treatment received in the trial, with long-term (9- and 18-month follow-ups) sleep, pain, depression, and fatigue outcomes, by comparing persons from all treatment groups whose sleep improved (improvers) to those whose sleep did not (non-improvers). This secondary analysis found that short-term improvements in sleep predicted long-term improvements for multiple measures of sleep, pain, and fatigue [6]. Conversely, short-term improvement in pain predicted long-term improvement in pain with marginal or non-significant long-term improvements in sleep, depression, and fatigue [6].

While the Lifestyles improvers study might be viewed as simply an “adjacent finding,” we believe it was a novel one and one that was worthy of replicating. Confirming these initial findings would be clinically relevant as it would add further evidence that improved sleep in this considerable fraction of the older adult population can have significant long-term benefits, regardless of how the short-term improvement in sleep is achieved.

We recently completed the “OATS” (OsteoArthritis and Therapy for Sleep) study, a randomized controlled trial of individual telephone-delivered CBT-I among older adults with comorbid chronic moderate to severe osteoarthritis pain and insomnia. Trial results showed that CBT-I resulted in short-term (2-month) improvements in sleep, pain, and fatigue and sustained, long-term (12-month) improvements in sleep and fatigue but not pain [7].

In order to gain a clearer sense of the long-term benefits of improved sleep (or pain) on comorbid conditions such as sleep, pain, depression, and fatigue, we conducted a secondary analysis of the OATS trial data, comparable to the previously reported Lifestyle “improvers” analysis. This approach of collapsing across treatment conditions and comparing the long term outcomes of short-term sleep (or pain) improvers versus non-improvers allows use of the full OATS study sample to compare persons with an improvement in insomnia (or in pain) to those without, thereby increasing the difference in 2-month change between comparison groups relative to the difference in insomnia (or pain) change in comparison to the OATS intervention groups as reported in the RCT. Our analyses assess whether

these amplified short-term differences in 2-month insomnia (or pain) improvement predict long-term sustained differences in 12-month outcomes (sleep, pain, depression, and fatigue). Here we report the results of these OATS study improver analyses.

Methods

The OATS trial was a randomized, controlled trial of six sessions of CBT-I versus an education-only attention control (EOC) over eight weeks, all delivered individually by telephone to improve sleep and secondary outcomes in older adults with clinically significant osteoarthritis (OA) pain and comorbid insomnia. The study was approved by the University of Washington institutional review boards. Study recruitment began in September 2016 and the last 12-month assessment was conducted in December 2018. Details describing OATS study design rationale, recruitment, screening, randomization procedures, and intervention protocols have been published elsewhere [7, 8], as have the primary outcome results from the post-treatment (2-month) and long-term (12-month) assessments [7].

Participants

Three hundred twenty-seven KPW members from across Washington State, age 60 or older were enrolled in the OATS trial (see Figure 1—OATS Consort Flow Chart). OATS participants were 60 years or older, continuously enrolled at KPW for at least one year, with a diagnosis of OA on at least one health care visit in the three years prior to screening. All study participants passed an initial screen using a 4-item version of the Insomnia Severity Index (ISI) [8, 9] and the Brief Pain Inventory—short form (BPI-sf) [10]. Persons with ISI ≥ 6 and two 0–10 pain rating (BPI-sf average pain intensity and interference) summed scores ≥ 9 at initial screening were invited to participate in the study. Three weeks later, to ensure insomnia and pain were chronic, potential subjects were re-screened by telephone to confirm eligibility and interest in participation. At this follow-up call, potential participants with a full 7-item ISI score ≥ 11 , a BPI-sf total score ≥ 9 , and a score of less than 7 on the Blessed Short Orientation Memory and Concentration Test [11] (indicating no cognitive impairment) were invited to participate. Exclusions included: primary sleep disorder diagnosis (other than insomnia), rheumatoid arthritis, active cancer, or congestive heart failure. Participants were not excluded because of other chronic illnesses, including psychiatric disorders, or because they were taking prescription or over-the-counter sleep or pain medications.

Comparison groups

For the current analyses, the 327 OATS trial participants, regardless of originally randomly assigned treatment arm, were defined as either sleep Improvers (a 30% or greater baseline to 2-month [post-treatment] reduction on the ISI) or Non-Improvers. Participants were similarly defined as pain Improvers and Non-Improvers using the same criterion on the BPI-sf. We employed this 30% or greater reduction criterion based on a convention established for defining clinically significant improvement in pain severity [12] and have used it previously to examine the impact of short-term improvements of sleep and pain in the Lifestyles trial sample [6].

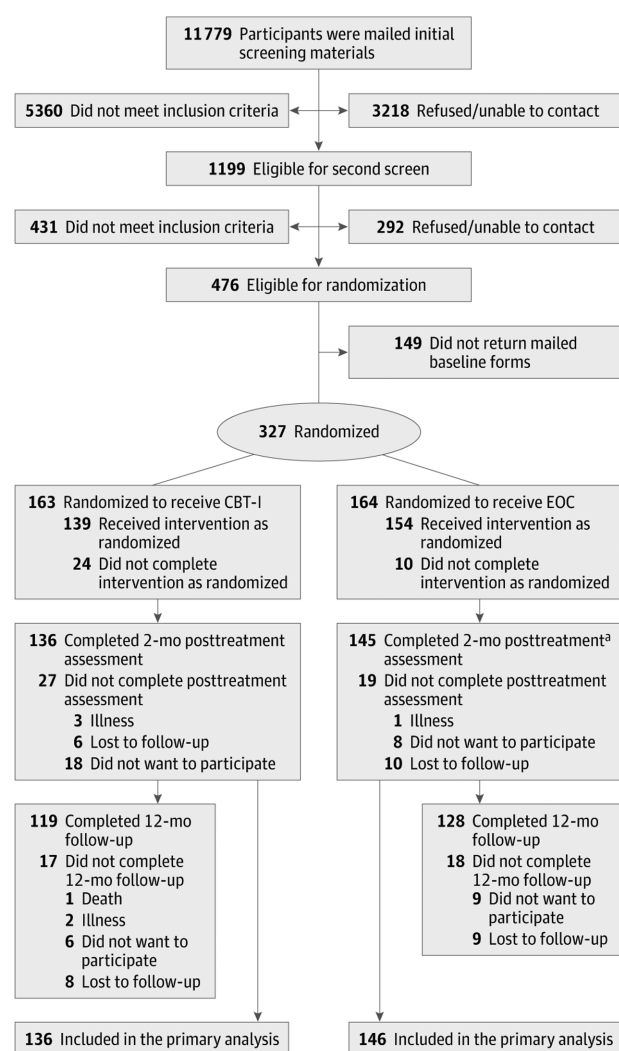


Figure 1. Participant recruitment and retention of telephone-delivered cognitive-behavioral therapy for insomnia (CBT-I) vs education only control (EOC) [7].

To facilitate the comparison of the results of our study with the broad insomnia literature, we further divided the OATS trial participants, again regardless of originally randomly assigned treatment arm, using two other ISI-based criteria more traditionally used in CBT-I trials [13, 14]. Subjects were divided into either Responders (ISI reduction of > 8 points from baseline to 2 or 12 months) versus Non-Responders, [13] or to Remitters (ISI < 7 at 2 or 12 months) versus Non-Remitters [14].

Data collection

Blinded assessments included primary outcome measures of insomnia and sleep quality, and secondary outcome measures of pain (BPI-sf total, Severity, and Interference scores), depression, and fatigue. Assessments were collected at baseline (before randomization), post-treatment (2-months), and longitudinal (12-months) follow-up.

Self-reported variables included age, sex, race, education, marital status, and duration of sleep and pain disturbances. Medication use (antidepressant, opioid, and sedative/hypnotic)

and Charlson Comorbidity Index (CCI) score were derived from electronic health records. Zip codes determined residence in medically underserved areas or health professional shortage areas (MU/HPSAs).

Outcomes

Insomnia. Insomnia Severity Index (ISI), a 7-item questionnaire assessing global insomnia severity. Items are rated 0–4 (total score range 0–28); 15 or higher is considered moderate to severe insomnia in clinical populations [9]. A score >10 is considered optimal for detecting insomnia cases in community samples, while ISI scores <7 identify insomnia remission [13, 14].

Sleep quality. Sleep quality was measured using the total score on the 19-item Pittsburgh Sleep Quality Index (PSQI) (possible range 0–21; higher is worse) [15].

Pain. Arthritis pain intensity and interference with activities were measured using the 11-item Brief Pain Inventory-short form (BPI-sf) [10]. The BPI-sf rates pain severity (4 items) and interference (7 items) from 0 to 10, with higher scores reflecting more pain severity and pain interference with life activities.

Depression. Depression was measured using the Patient Health Questionnaire (PHQ-8) [16]. The PHQ-8 rates frequency of occurrence of 8 depressive symptoms on a 4-point scale. Scores of 5–9 indicate mild or subclinical depression; 10 or greater indicate depression [17, 18]. The single item of the PHQ-8 asking about sleep problems was removed and a PHQ-7 was used in these analyses.

Fatigue. Fatigue was measured using the Flinders Fatigue Scale (FFS), a 7-item self-report questionnaire measuring fatigue level in a variety of situations; higher is worse [19]. The single item of the FFS mentioning sleep problems was removed and a FFS-6 was used in these analyses.

Baseline covariates

Patient characteristics. Age, sex, and chronic illness comorbidity, education, retirement status, race, and whether participants lived in a MU/HPSA were collected from KPW electronic medical records and baseline OATS participant self-report in the baseline interview.

Mental status. Cognitive impairment was assessed using the Blessed Short Orientation Memory and Concentration Test [11] collected at baseline.

Comorbidity. The burden of comorbid illnesses was assessed using the Charlson Comorbidity Index (CCI) derived from electronic health records. The CCI is a weighted index that takes into account the number and the seriousness of an individual's comorbid illnesses and has been updated for use with ICD-10 codes [20].

Medication use. Antidepressant, opioid, and sedative/hypnotic medication use was assessed using electronic health records.

Data analysis

Overall, at the conclusion of the trial approximately 86% and 76% of those randomized had a recorded ISI (primary outcome) measure at 2- and 12-months, respectively. To utilize the entire randomized cohort and to address missing outcome data due to study attrition, multiple imputations were used to create the analytic dataset for the analyses conducted in this manuscript. Further details regarding missing outcome data, including summaries by treatment arm, have been published elsewhere [7]. The method of imputation by chained equations was used to generate an analytic dataset comprising ten imputations [21]. In concert with the methodology applied in the main analysis, observed baseline characteristics and outcome measures for those randomized were utilized in imputation models, including randomization group, age, sex, race/ethnicity, marital status, level of education, self-reported duration of sleep problems, self-reported number of days of pain in the last year, residence in an MU/HPSA, the CCI, baseline use of opioids, hypnotics or antidepressants, and baseline values of the study outcomes (insomnia, sleep, pain, depression, and fatigue). Imputations were performed in SAS v9.4 (SAS Institute, Inc) for Microsoft Windows using IVEWare: Imputation and Variance Estimation Software, version 0.3 (University of Michigan).

We report proportions to describe categorical variables and means and standard deviations for continuous variables at baseline, combining estimates from each imputed dataset using the methodology set forth by Rubin (aka Rubin's rules) [22]. Outcomes including sleep, pain, depression, and fatigue for Improvers and Non-improvers were compared at baseline, 2-months, and 12-months. At baseline, Improvers and Non-improvers were compared on all covariates and all outcome variables using logistic regression, with estimates combined across imputations. P-values for continuous and dichotomous variables were estimated using Rubin's rules. For categorical variables with more than two categories, p-values were obtained using the method of Meng and Rubin [23]. Unadjusted mean estimates on outcome variables were compared at 2-months between Improvers and Non-improvers using independent t-tests and Cohen's *d* combining over imputed dataset [24]. To assess differences in long-term outcomes (12 months) between Improvers and Non-improvers, multivariate linear regression models were fit to each imputed dataset adjusted for intervention arm, age, sex, baseline antidepressant, analgesic and sedating medication use, and baseline values of relevant outcome. Given the findings in the univariate models, additional covariates including education, baseline values of the PHQ-7, and BPI interference were added in the Sleep Improver models. Model estimates were combined across imputed datasets using Rubin's rules. Cohen's *f*² [24] was estimated and averaged over imputed datasets to measure the effect size of improver status within the context of multivariate regression.

Because our operational definition of Sleep Improvers is not standardly used in the insomnia literature, we conducted a sensitivity analysis defining study groups using recognized criteria for a clinically meaningful response to treatment (ISI drop of > 8 points from baseline to 2-month assessment) as Responders and Non-responders [13].

All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC) and R version 4.0.3.

Results

The OATS trial included 327 participants assigned to the two experimental arms (Figure 1). Among these 327 trial participants, combining all 10 imputations, at 2-month follow-up 63.3% of the participants (79.7% of the CBT-I and 46.9% of the EOC groups) were classified as Sleep Improvers and 36.7% (20.3% of the CBT-I and 53.1% of the EOC groups) as Sleep Non-Improvers; 37.7% of the participants (44.8% of CBT-I and 30.6% of the EOC groups) were classified as Pain Improvers and 62.3% (55.2% of CBT-I and 69.4% of the EOC groups) as Pain Non-Improvers.

Baseline descriptive statistics for the demographic, general health, drug use, and sleep, pain, depression, and fatigue measures for Sleep Improvers versus Non-Improvers are reported in Table 1. The two groups did not differ at baseline except for higher PHQ-7 depression scores among Sleep Non-Improvers relative to Sleep Improvers, 5.5 (3.3) versus 4.6 (3.3), respectively ($p = .04$). Table 2 reports baseline characteristics for Pain Improvers versus Non-Improvers. The Pain groups were comparable on almost all baseline measures. The sole baseline difference between the pain groups was a higher percentage of opioid users in the Pain Non-Improvers relative to Pain Improvers, 24.2% versus 11.4%, respectively ($p = .01$).

Table 3 compares the 2-month (post-treatment) unadjusted means and standard deviations for Sleep Improvers versus Non-Improvers and the Pain Improvers versus Non-Improvers for measures of sleep, pain, depression, and fatigue. As expected, the Sleep Improvers had lower 2-month ISI scores compared to sleep Non-Improvers ($p < .01$), as ISI was the criterion variable for determining the groups. Sleep Improvers as a group showed a reduction in ISI of 6.8. The Sleep Improvers also had more favorable overall sleep quality (PSQI), pain (BPI-sf total score and severity and interference subscales), depression (PHQ-7), and fatigue (FFS-6) scores relative to Sleep Non-Improvers (all p values $< .01$). Pain Improvers had lower BPI-sf (the group assignment criterion variable) scores compared to Pain Non-Improvers ($p < .01$). The Pain Improvers also had improved sleep (ISI and PSQI), pain (BPI-sf total scores and severity and interference subscales), depression, and fatigue scores relative to the Pain Non-Improvers (all p values $< .01$). The effect sizes (Cohen's *d* [24]) for short-term improvements in sleep, pain, depression, and fatigue for the Sleep Improvers were all large (Cohen's $d > 0.8$, Table 3). The effect sizes for short-term improvements in insomnia symptoms and pain for Pain Improvers were large, while those for general sleep quality, depression, and fatigue were medium (Cohen's $d > 0.5$, Table 3).

Table 4 reports the 12-month outcomes in sleep, pain, depression, and fatigue and adjusted mean differences, 95% confidence intervals, and Cohen's *f*² (effect size) statistics [24] by Sleep Improver and Pain Improver status. Sleep Improvers showed sustained improvements at 12 months for all examined measures of sleep, pain, depression, and fatigue compared to Sleep Non-Improvers. Pain Improvers showed significant sustained improvements at 12 months for all measures of sleep, pain, depression, and fatigue compared to pain Non-Improvers (all p values $< .01$ except PHQ-7 and FFS-6). The effect sizes (Cohen's *f*²) for the sustained improvements in the measures examined for Sleep Improvers ranged from 0.17 to 0.04 while those for Pain Improvers ranged from 0.12 to 0.03 (Table 4). All of these observed effect sizes for sustained improvement in measures were small (Cohen's *f*² < 0.15) with the exception of sustained improvement in insomnia symptoms, which was medium (0.17) (Table 4).

Table 1. Baseline characteristics by Sleep Improver status, full randomized sample (n = 327)

Baseline characteristic	Sleep improver	Sleep non-improver	P value*
Percent of sample (%)	63.3	36.7	
Age	70.2 (7.1)	70.2 (6.3)	.98
Female (%)	78.2	68.4	.07
Race (%)			.21
White, Non-Hispanic	84.2	76.4	
Hispanic	2.9	6.7	
Non-White	13.0	16.8	
Education (%)			.11
No/some college	48.2	57.7	
College graduate or higher	51.8	42.3	
Marital status (%)			.34
Married/living with partner	67.9	62.5	
Single/divorced/living alone/unknown	32.1	37.5	
Living in MU/HPSA (%)	64.2	67.5	.56
Charlson Comorbidity Index score (%)			.57
0	62.5	61.4	
1	18.7	15.3	
2+	18.8	23.3	
Anti-depressants use (%)	15.4	16.0	.89
Opioid use (%)	20.1	18.7	.76
Sedative/hypnotic use (%)	5.6	5.4	.95
Blessed Short Orientation Memory and Concentration Mental Status Test	2.2 (1.9)	2.4 (2.1)	.37
Insomnia Severity Index (ISI)	15.6 (3.4)	15.3 (3.1)	.46
Pittsburgh Sleep Quality Index (PSQI)	11.5 (3.0)	11.7 (3.1)	.62
Brief Pain Inventory-short form (BPI-sf)	9.3 (2.9)	9.9 (3.1)	.14
BPI Severity	4.6 (1.5)	4.8 (1.6)	.31
BPI Interference	4.8 (1.8)	5.1 (1.9)	.12
Patient Health Questionnaire (PHQ-7)	4.6 (3.5)	5.5 (3.3)	.04
Flinders Fatigue Scale (FFS-6)	11.5 (5.1)	12.1 (4.8)	.37

*p values correspond to estimated effect of Improvement status from univariate logistic regression models for the baseline values. Standard errors were adjusted to account for multiple imputations.

A sensitivity analysis dividing the study sample by short-term sleep improvement using a recognized criterion [13] for clinically significant improvement in sleep (ISI drop of > 8 points from baseline to 2-month assessment) into Responders and Non-responders and examining long-term improvements in sleep, pain, depression, and fatigue yielded comparable results to the main analyses, with short-term improvements in sleep predicting long-term improvements in the outcome measures. The results of the sensitivity analysis are reported in [Supplementary Tables S1–S3](#).

We also compared the short and long-term improvements in sleep by group, based on three criteria for improvement (30% reduction of ISI from baseline to 2 months (Improvers), ISI drop of > 8 from baseline to 2 months (Responders), and ISI < 7 at 2 months (Remitters). These comparisons are shown in [Table 5](#). Classification using the more liberal criterion of Improver compared to Responder and Remitter resulted in assignment of consistently higher percentages of the sample across the 2 month, 12 month, both 2 and 12 month, not 2 but 12 month, and at 2 but not at 12 month conditions. The Responders and Remitters criteria classified consistently lower but very comparable percentages of the sample across conditions. All three criteria demonstrated the sustainability of short-term improvements of sleep regardless of how short-term improvement was defined.

Discussion

At 12 months, Sleep Improvers reported clinically significant sustained improvement on multiple measures of self-reported

sleep (insomnia symptoms and general sleep quality) as well as sustained but less robust improvements in self-reported pain, depression, and fatigue relative to Sleep Non-Improvers (see [Table 4](#)). Study participants defined as Pain Improvers showed a similar pattern of results with both 2- and 12-month self-reported improvements in pain as well as in sleep, depression, and fatigue relative to Pain Non-Improvers. This pattern of sustained improvements was consistent with the short-term improvements in these measures observed for both Sleep and for Pain Improvers relative to their respective Non-Improvers (see [Table 3](#)).

Tang et al. [3] in their systematic review and meta-analysis examining nonpharmacological treatments of insomnia in patients with chronic pain conditions reported that “nonpharmacological sleep treatments in chronic pain patients were associated with a large improvement in sleep quality, ... small reduction in pain, ... and moderate improvement in fatigue ... at posttreatment ... The effects on sleep quality and fatigue were maintained at follow-up (up to 1 year) when a moderate reduction in depression ... was also observed” (p. 1751). Similarly, Benz et al. [2] in their systematic review and meta-analysis of CBT-I impact on daytime symptoms reported that, “results suggest that CBT-I is effective in the treatment of daytime symptoms, albeit with predominantly small to moderate effects compared to far stronger effects on the core symptoms of insomnia” (p. 1). Our findings are consistent with those summarized in these meta-analyses by both Tang et al. and Benz et al.

Our study findings are supportive of a bidirectional relationship between sleep and pain. We found that short-term

Table 2. Baseline characteristics by Pain Improver status, full randomized sample (n = 327)

Baseline characteristic	Pain improver	Pain non-improver	P value*
Percent of sample (%)	37.7	62.3	
Age	70.1 (6.8)	70.3 (6.8)	.79
Female (%)	78.8	72.1	.21
Race (%)			.74
White, Non-Hispanic	79.1	82.7	
Hispanic	5.1	3.8	
Non-White	15.8	13.5	
Education (%)			.55
No/some college	49.4	53.0	
College graduate or higher	50.6	47.0	
Marital status (%)			.20
Married/living with partner	70.4	63.2	
Single/divorced/living alone/unknown	29.6	36.8	
Living in MU/HPSA (%)	61.2	68.0	.25
Charlson Comorbidity Index score (%)			.71
0	62.9	61.6	
1	15.2	18.8	
2+	21.9	19.6	
Anti-depressants use (%)	11.7	18.0	.14
Opioid use (%)	11.9	24.2	.01
Sedative/hypnotic use (%)	5.4	5.6	.93
Blessed Short Orientation Memory and Concentration Mental Status Test	2.2 (2.0)	2.3 (2.0)	.50
Insomnia Severity Index(ISI)	15.5 (3.5)	15.5 (3.1)	.98
Pittsburgh Sleep Quality Index (PSQI)	11.4 (3.2)	11.7 (3.1)	.46
Brief Pain Inventory—short form (BPI-sf)	9.7 (3.1)	9.4 (2.9)	.44
BPI Severity	4.7 (1.6)	4.6 (1.5)	.61
BPI Interference	5.0 (1.8)	4.8 (1.8)	.41
Patient Health Questionnaire (PHQ-7)	4.8 (3.6)	5.0 (3.3)	.69
Flinders Fatigue Scale (FFS-6)	11.4 (5.1)	11.9 (4.9)	.44

*p values correspond to estimated effect of Improvement status from univariate logistic regression models for the baseline values. Standard errors were adjusted to account for multiple imputations.

Table 3. Two-month outcomes by Sleep Improver and Pain Improver status, full randomized sample (n = 327)

	Improver	Non-improver	P value*	Cohen's d**
SLEEP				
Insomnia Severity Index	6.7 (3.2)	13.5 (2.9)	<.01	-2.25
Pittsburgh Sleep Quality Index	6.4 (3.1)	10.3 (3.3)	<.01	-1.24
Brief Pain Inventory-short form	6.3 (3.2)	9.6 (3.3)	<.01	-1.04
BPI Severity	3.4 (1.7)	4.7 (1.8)	<.01	-0.76
BPI Interference	2.9 (1.8)	4.9 (1.9)	<.01	-1.12
Patient Health Questionnaire	2.5 (2.6)	4.9 (3.0)	<.01	-0.88
Flinders Fatigue Scale	7.1 (4.9)	11.2 (5.2)	<.01	-0.82
PAIN				
Insomnia Severity Index	6.8 (3.7)	10.7 (4.3)	<.01	-0.95
Pittsburgh Sleep Quality Index	6.3 (3.2)	8.7 (3.7)	<.01	-0.67
Brief Pain Inventory	4.5 (2.3)	9.3 (2.9)	<.01	-1.76
Brief Pain Inventory Severity	2.5 (1.2)	4.7 (1.6)	<.01	-1.51
Brief Pain Inventory Interference	2.0 (1.4)	4.6 (1.8)	<.01	-1.58
Patient Health Questionnaire	2.4 (2.5)	4.0 (3.1)	<.01	-0.54
Flinders Fatigue Scale	6.6 (4.6)	9.9 (5.5)	<.01	-0.64

*p values correspond to estimated effect of Improvement status in t-test for the 2-month values. Standard errors were adjusted to account for multiple imputations.

**Cohen's d > 0.2, 0.5 and 0.8 represent small, medium and large effect sizes, respectively

improvements in sleep or pain were both associated with long-term in sleep, pain, depression, and fatigue. On average, the long-term improvements were of small effect size, with the exception of medium effect size for sustained insomnia symptom reduction for Sleep Improvers (see Table 4). Nevertheless, short-term improvements in both sleep and pain each consistently predicted long-term health benefits

across the four domains of sleep, pain, depression, and fatigue (Table 4).

It is also of interest that, regardless of whether the study sample was divided by short-term improvement in either sleep or pain, the resulting groups were remarkably similar on most baseline variables. The similarities within both the sleep and pain improvement defined groups suggest that there is little at

Table 4. Twelve-month outcomes by Sleep Improver and Pain Improver status, full randomized sample ($n = 327$)

	Improver	Non-improver	Adjusted mean difference***	95% confidence interval	Cohen's f^{****}
SLEEP*					
Insomnia Severity Index	9.1	12.7	-3.5	(-4.6, -2.5)	0.17
Pittsburgh Sleep Quality Index	7.9	10.2	-2.2	(-3.1, -1.4)	0.11
Brief Pain Inventory—short form	6.8	8.4	-1.6	(-2.4, -0.7)	0.05
BPI Severity	3.5	4.2	-0.7	(-1.2, -0.3)	0.05
BPI Interference	3.3	4.2	-0.9	(-1.3, -0.4)	0.04
Patient Health Questionnaire	3.8	5.0	-1.2	(-2.0, -0.4)	0.05
Flinders Fatigue Scale	8.1	10.3	-2.2	(-3.3, -1.1)	0.06
PAIN**					
Insomnia Severity Index	8.8	11.1	-2.4	(-3.4, -1.3)	0.08
Pittsburgh Sleep Quality Index	7.9	9.2	-1.3	(-2.2, -0.4)	0.04
Brief Pain Inventory-short form	5.7	8.0	-2.3	(-3.1, -1.5)	0.12
BPI Severity	3.0	4.1	-1.1	(-1.5, -0.7)	0.12
BPI Interference	2.8	4.0	-1.2	(-1.7, -0.7)	0.09
Patient Health Questionnaire	3.7	4.5	-0.8	(-1.5, -0.2)	0.03
Flinders Fatigue Scale	7.9	9.4	-1.5	(-2.7, -0.4)	0.03

*Means and mean differences adjusted for baseline value of relevant outcome, intervention arm, age, sex, education, baseline antidepressant, analgesic and sedating medication use and baseline values of PHQ, BPI interference.

**Means and mean differences adjusted for baseline value of relevant outcome, intervention arm, age, sex, baseline antidepressant, analgesic and sedating medication.

***All comparisons $p < .01$.

****Cohen's $f^2 \geq 0.02, 0.15$, and 0.35 represent small, medium, and large effect sizes, respectively.

Table 5. The percentages of the study sample ($n = 327$) who met criterion* as Improvers, Responders, or Remitters: at 2 months, at 12 months, at both 2 and 12 months, at 12 but not 2 months, and at 2 but not 12 months

	Improvers	Responders	Remitters
2 Months	63.3	37.7	38.9
12 Months	61.1	38.8	36.5
Met criterion at both 2 and 12 months	48.5	27.6	25.4
Met criterion at 12 but not 2 months	12.6	11.2	11.1
Met criterion at 2 but not 12 months	14.8	10.2	13.4

*Improvers = 30% reduction in ISI from baseline to 2 or 12 months;

Responders = ISI reduction of > 8 from baseline to 2 or 12 months;

Remitters = ISI < 7 at 2 or 12 months.

baseline to distinguish those who do show short- and long-term improvement in either sleep or pain from those who do not.

The current study has weaknesses. It is a secondary analysis of data gathered in a randomized controlled trial. As such, it can only describe associations and not ascribe causal relationships among the variables reported. The rationale for comparing improvers to non-improvers is that it increases the magnitude of the change in variables of interest relative to differences between CBT-I and control subjects where intervention benefits are heterogeneous across subjects. However, the non-experimental comparisons reported here may be biased by unmeasured confounding that led to both improved short-term sleep or pain outcomes. As an example, while baseline use of analgesics and hypnotics and depression were covariates in the analyses of long-term outcomes, changes in any medication scheduling or dosing over time were not analyzed which might have influenced results.

Nevertheless, the current study also has considerable strengths. The OATS study employed a large, well-characterized

study sample of a primary care population of older adults with chronic moderate to severe OA pain and insomnia with long-term follow-up assessment [7, 8]. The trial had good subject retention (75% at 12 months). The approach of collapsing across treatment conditions and comparing the long term outcomes of short-term sleep (or pain) improvers versus non-improvers allows use of the full OATS study sample to compare persons with a large improvement in insomnia (or in pain) to those without, capitalizing on increasing the difference in 2-month change between comparison groups. Finally, the analytic design involved assigning participants' improver status based on ISI or BPI-sf change from baseline to 2-month assessment, while sustained outcomes of Improvers and Non-Improvers were analyzed using 12 month data with baseline data as covariates, providing a time-order to the observed relationships.

These secondary analyses of the OATS trial findings demonstrated that OA patients with comorbid pain and insomnia whose sleep improved in the short-term (2 months) were likely to show continued long-term (12 months) improvement in both insomnia symptoms (ISI) and general sleep quality (PSQI). These sustained improvements in sleep were accompanied by associated benefits in pain, depression, and fatigue outcomes relative to OA patients whose sleep did not improve short-term. OA patients whose pain improved short-term showed a similar pattern of improvement with both 2- and 12-month self-reported improvements in pain as well as in sleep, depression, and fatigue. Comparable sustained improvements were observed for OA patients whose pain improved short-term, supporting an association between sleep and pain in this population.

Overall, these findings are consistent with our previous examination of sleep and pain improver status in the Lifestyles study, [6] findings of a recent systematic review and meta-analysis of nonpharmacological treatments of insomnia in patients with chronic pain conditions [3] and of a very recent systematic review and meta-analysis of CBT-I's beneficial impact on daytime symptoms [2]. However, while the current OATS study found

that short-term improvements in both sleep and pain each were associated with long-term improvements in multiple outcomes, Lifestyles found that short-term sleep improvements were associated with greater long-term improvements than were short-term pain improvements. This difference in findings may be attributable to a major difference between the two study samples. In Lifestyles, the severity of the sleep and pain complaints of the study sample were relatively mild, and because Lifestyles did not employ a double screen to ensure relative chronicity of sleep and pain complaints, both showed regression to the mean between the single screen and the study baseline assessment. In contrast, the OATS study sample was specifically recruited and double screened to have moderate to severe sleep and pain complaints that were chronic. These sample differences in severity and chronicity of sleep and pain symptomology at baseline may help explain the comparability of the long-term associated benefits of short-term improvement in both sleep and pain in the current study.

In conclusion, our findings support previous findings that successful resolution of asleep disturbance in pain populations with comorbid insomnia may yield benefits not only for long-term improvement in sleep but also for reduced pain over the long-term, along with associated improvements in depression and fatigue. This may be particularly salient given that commonly prescribed drug therapies for controlling chronic pain (e.g. NSAIDs and opioids) have clinically significant and potentially life-threatening adverse effects, particularly among older adults, and often less than desired analgesic efficacy. Successfully improving sleep in older adults presenting with osteoarthritis-related chronic insomnia and pain, and perhaps other similar pain populations, may well have the additional benefits of sustained improvements in pain, depression, and fatigue.

Supplementary Material

Supplementary material is available at SLEEP online.

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Data Availability

The data underlying this article will be shared on reasonable request to the corresponding author.

References

1. Wu JQ, et al. Cognitive behavioral therapy for insomnia comorbid with psychiatric and medical conditions: a meta-analysis. *JAMA Intern Med.* 2015;175(9):1461–1472.
2. Benz F, et al. The efficacy of cognitive and behavior therapies for insomnia on daytime symptoms: A systematic review and network meta-analysis. *Clin Psychol Rev.* 2020;80:101873.
3. Tang NK, et al. Nonpharmacological treatments of insomnia for long-term painful conditions: a systematic review and meta-analysis of patient-reported outcomes in randomized controlled trials. *Sleep.* 2015;38(11):1751–1764. doi:10.5665/sleep.5158
4. McCurry SM, et al. Who benefits from CBT for insomnia in primary care? Important patient selection and trial design lessons from longitudinal results of the Lifestyles trial. *Sleep.* 2014;37(2):299–308. doi:10.5665/sleep.3402
5. Vitiello MV, et al. Cognitive-behavioral treatment for comorbid insomnia and osteoarthritis pain in primary care: the lifestyles randomized controlled trial. *J Am Geriatr Soc.* 2013;61(6):947–956.
6. Vitiello MV, et al. Short-term improvement in insomnia symptoms predicts long-term improvements in sleep, pain, and fatigue in older adults with comorbid osteoarthritis and insomnia. *Pain.* 2014;155(8):1547–1554.
7. McCurry SM, et al. Effect of telephone cognitive behavioral therapy for insomnia in older adults with Osteoarthritis Pain: a randomized clinical trial. *JAMA Intern Med.* 2021;181(4):530–538.
8. McCurry SM, et al. Telephone interventions for co-morbid insomnia and osteoarthritis pain: The OsteoArthritis and Therapy for Sleep (OATS) randomized trial design. *Contemp Clin Trials.* 2019;87:105851.
9. Bastien CH, et al. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. *Sleep Med.* 2001;2(4):297–307.
10. Cleeland CS, et al. Pain assessment: global use of the Brief Pain Inventory. *Ann Acad Med Singap.* 1994;23(2):129–138.
11. Katzman R, et al. Validation of a short orientation-memory-concentration test of cognitive impairment. *Am J Psychiatry.* 1983;140(6):734–739.
12. Dworkin RH, et al. Interpreting the clinical importance of group differences in chronic pain clinical trials: IMMPACT recommendations. *Pain.* 2009;146(3):238–244.
13. Morin CM, et al. The Insomnia Severity Index: psychometric indicators to detect insomnia cases and evaluate treatment response. *Sleep.* 2011;34(5):601–608. doi:10.1093/sleep/34.5.601
14. Yang M, et al. Interpreting score differences in the Insomnia Severity Index: using health-related outcomes to define

- the minimally important difference. *Curr Med Res Opin.* 2009;25(10):2487–2494.
15. Buysse DJ, et al. Quantification of subjective sleep quality in healthy elderly men and women using the Pittsburgh Sleep Quality Index (PSQI). *Sleep.* 1991;14(4):331–338. <https://pubmed.ncbi.nlm.nih.gov/1947597/>
 16. Kroenke K, et al. The PHQ-8 as a measure of current depression in the general population. *J Affect Disord.* 2009;114(1-3):163–173.
 17. Kroenke K, et al. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med.* 2001;16(9):606–613.
 18. Manea L, et al. Optimal cut-off score for diagnosing depression with the Patient Health Questionnaire (PHQ-9): a meta-analysis. *CMAJ.* 2012;184(3):E191–E196.
 19. Gradisar M, et al. The Flinders Fatigue Scale: preliminary psychometric properties and clinical sensitivity of a new scale for measuring daytime fatigue associated with insomnia. *J Clin Sleep Med.* 2007;3(7):722–728.
 20. Deyo RA, et al. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol.* 1992;45(6):613–619.
 21. Raghunathan TE, et al. A multivariate technique for multiply imputing missing values using a sequence of regression models. *Surv Methodol.* 2001;27(1):85–95.
 22. Rubin DB. *Multiple Imputation for Nonresponse in Surveys.* New York: John Wiley & Sons; 2004.
 23. Meng X-L, et al. Performing likelihood ratio tests with multiply-imputed data sets. *Biometrika.* 1992; 79(1):103–111.
 24. Cohen JE. *Statistical Power Analysis for the Behavioral Sciences.* Hillsdale, NJ: Lawrence Erlbaum Associates; 1988.