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Authors

Goforth, Harold W
Preud'homme, Xavier A
Krystal, Andrew D

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A Randomized, Double-Blind, Placebo-Controlled Trial of Eszopiclone for the Treatment of Insomnia in Patients with Chronic Low Back Pain

Harold W. Goforth, MD[1]; Xavier A. Preud'homme, MD[2]; Andrew D. Krystal, MD, MS[1]

[1]Assistant Professor of Medicine and Psychiatry, Duke Insomnia and Sleep Research Program, Duke University Medical Center; Attending Physician (GRECC), Durham Veterans Affairs Medical Center, Durham, NC; [2]Assistant Professor of Medicine and Psychiatry, Duke Insomnia and Sleep Research Program, Duke University Medical Center, Durham, NC; [3]Professor of Psychiatry and Director, Duke Insomnia and Sleep Research Program, Duke University Medical Center, Durham, NC

Study Objectives: Insomnia, which is very common in patients with chronic low back pain (LBP), has long been viewed as a pain symptom that did not merit specific treatment. Recent data suggest that adding insomnia therapy to pain-targeted treatment should improve outcome; however, this has not been empirically tested in LBP or in any pain condition treated with a standardized pain medication regimen. We sought to test the hypothesis that adding insomnia therapy to pain-targeted treatment might improve sleep and pain in LBP.

Design: Double-blind, placebo-controlled, parallel-group, 1-mo trial.

Setting: Duke University Medical Center Outpatient Sleep Clinic.

Patients: Fifty-two adult volunteers with LBP of at least 3 mo duration who met diagnostic criteria for insomnia (mean age: 42.5 y; 63% females).

Interventions: Subjects were randomized to eszopiclone (ESZ) 3 mg plus naproxen 500 mg BID or matching placebo plus naproxen 500 mg twice a day.

Measurements and Results: ESZ significantly improved total sleep time (mean increase: ESZ, 95 min; placebo, 9 min) (primary outcome) and nearly all sleep measures as well as visual analog scale pain (mean decrease: ESZ, 17 mm; placebo, 2 mm) (primary pain outcome), and depression (mean Hamilton Depression Rating Scale improvement ESZ, 3.8; placebo, 0.4) compared with placebo. Changes in pain ratings were significantly correlated with changes in sleep.

Conclusions: The addition of insomnia-specific therapy to a standardized naproxen pain regimen significantly improves sleep, pain, and depression in patients with chronic low back pain (LBP). The findings indicate the importance of administering both sleep and pain-directed therapies to patients with LBP in clinical practice and provide strong evidence that improving sleep disturbance may improve pain.

Trial Registration: clinicaltrials.gov identifier: NCT00365976

Keywords: insomnia, low back pain, eszopiclone

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INTRODUCTION

Chronic low back pain (LBP) is among the most prevalent of all health complaints.[1] Approximately 25% of the US population report experiencing at least 1 day of low back pain in the prior 3 mo and 7.6% report severe back pain in the past year.[2,3] LBP is also associated with substantial health care and productivity costs, reduced quality of life and function, and is commonly associated with insomnia.[1–4] A recent study reported that 78% of patients with chronic LBP experience insomnia and, of these, in 64% of cases the insomnia was caused by the LBP.[4] Although the long-standing view has been that this insomnia is a symptom of the pain, a growing body of literature suggests that insomnia might have important independent effects on the clinical course of pain syndromes.[5] Although pain may disrupt sleep, it appears that problems with sleep increase pain. The emerging point of view is that specific treatment for both pain and insomnia is needed for optimal clinical management.[5,6] However, there is minimal research evaluating whether this is, in fact, the case.

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Address correspondence to: Andrew D. Krystal, MD, MS, Duke University Medical Center, Trent Drive Room 54221, Durham, NC 27710; Tel: (919) 681-8728; E-mail: kryst001@mc.duke.edu

Two double-blind, placebo-controlled studies have been carried out regarding the pharmacologic treatment of insomnia in patients with chronic pain. In both, the pain condition studied was rheumatoid arthritis.[7,8] One crossover study (n = 15) found that triazolam added to the clinical pain regimen improved total sleep time (TST) and morning stiffness but not objective sleep measures, pain severity, or other arthritis outcomes compared with placebo.[7] In a parallel group study (n = 153) in which subjects were maintained on their ongoing "disease modifying" clinical treatments and allowed pain medications only if pain worsened during the trial, eszopiclone (ESZ) 3 mg led to significant improvement of all sleep outcomes and some rheumatoid arthritis measures compared with placebo.[8]

Several trials also evaluated the addition of cognitive behavioral therapy for insomnia (CBTI) to the ongoing clinical pain management regimen.[9–12] In one, 60 patients with a heterogenous set of chronic pain conditions were randomized to group CBTI or waitlist.[9] Improvements in sleep but not pain were noted. In another study,[11] CBTI improved some pain measures and the pain subscale of the Short Form-36 but not the McGill Pain Questionnaire compared with baseline in a *post hoc* analysis of data from 51 individuals with osteoarthritis.[11,12] Comparisons with the control therapy were not reported. Last, in 28 patients with "nonmalignant pain originating in the spine," CBTI improved sleep and the Multidimensional Pain Inventory "interference" scale, but not the "pain severity" scale, the Pain Disability Index, or average daily pain ratings

compared with a control condition in which subjects reviewed sleep/pain diary and Beck Depression Inventory data from the prior week.[9]

The available studies represent a limited set of assessments of the treatment of insomnia occurring with a few pain conditions that were generally not treated with standardized pain regimens. In these studies, either no pain-directed therapy was administered, subjects remained on whatever interventions they may have received as part of usual clinical care, or a behavioral pain regimen was added to the medication regimen that they received as part of clinical care. Most of these studies were small and likely underpowered, and several of these studies were not blinded treatment trials or did not include a validated control intervention. Thus, existing studies provide limited evidence of the efficacy of insomnia therapy in patients with insomnia co-occurring with pain syndromes and have yet to address the critical clinical issue of whether adding insomnia-specific therapy to pain-targeted therapy improves outcomes.

Therefore, we sought to carry out a double-blind placebo-controlled trial of insomnia therapy in patients with chronic pain treated with a standardized pain medication regimen. We also sought to carry out the first double-blind placebo-controlled study of insomnia treatment in patients with LBP. Surprisingly, despite the fact that LBP is the most common pain condition, the treatment of insomnia in this disorder has never been the focus of a clinical trial. We tested the hypothesis that the administration of insomnia therapy with the hypnotic medication ESZ along with pain management with naproxen 500 mg twice a day statistically significantly improves treatment outcome compared with pain management alone (placebo plus naproxen).

METHODS

Design

This study, approved by the Duke Institutional Review Board, was a single-site, 1-mo, parallel-group, placebo-controlled study of 3 mg ESZ versus placebo (PBO) in patients with LBP treated with naproxen (NAP) 500 mg twice daily and lansoprazole (LAN) 15 mg daily. There was an initial screening visit (obtained informed consent, history and physical examination, screening depression, insomnia, and pain assessments; pregnancy testing; serum chemistries; complete blood count; prothrombin time/partial thromboplastin time/international normalized ratio; urinalysis; and urine drug screen) where qualifying subjects were switched from their current pain regimen to NAP and LAN. NAP and LAN was chosen as the pain therapy because this is one of the regimens recommended for first-line treatment of LBP in published clinical practice guidelines.[3] They returned 1 w later for repeat urine drug screen, and training on entering diary data and baseline data collection. Those continuing to qualify were randomized to receive ESZ or PBO by mouth approximately 30 min prior to lights out in addition to ongoing therapy with NAP and LAN. Subjects returned for two visits at w 1 and 2 of double-blind treatment for a pill check; urine drug screen; adverse events monitoring; pain, function, and sleep assessments; and distribution of double-blind study medications. Final outcome and safety assessments, history and physical examination, repeat of screening laboratory tests and closeout occurred after 1 mo of double-blind treatment. During screening, subjects were told to continue their current sleep behaviors/patterns throughout the study and no advice was given to subjects about their sleep patterns or behaviors at any time during the study.

Randomization

The random allocation schedule was generated by the sponsor based on a computer-derived pseudorandom number generator (1:1 randomization ratio). The sponsor also supplied identical ESZ and PBO capsules and provided the investigators with sequentially numbered pill containers in order to implement the random allocation sequence. So that all investigators remained blind to treatment assignment throughout the study, the random allocation sequence was only provided to the investigators by the sponsor after all subjects had completed the study.

Participants

Participants were recruited through newspaper advertisements, posted announcements, and physician referrals. All included in this trial met the following criteria: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision diagnosis of insomnia because of a general medical condition (LBP)[13]; insomnia did not predate LBP onset by more than 1 mo; based on a sleep history taken by the study psychiatrist, the subject had a usual nightly TST less than 6.5 h and/or usual sleep onset latency (SOL) more than 30 min for the month prior to screening; Insomnia Severity Index (ISI) greater than14 (at least moderate insomnia); were 21–64 y of age; visual analog scale (VAS) pain greater than 40; Patient Global Impression (PGI) Pain greater than 2 (at least moderate severity); more back pain than leg pain; no signs of spinal nerve root compression; normal motor strength on physical exam; LBP duration longer than 3 mo; pain inferior to T12 and superior to the gluteal fold. These inclusion criteria were based on prior placebo-controlled studies of ESZ including the prior study in patients with rheumatoid arthritis.[8,14–21]

We excluded those with: significant medical or neurological illness other than LBP (based on history, physical examination, and laboratory test review by the study psychiatrist); psychiatric disease with substantive impact on sleep currently or in the past 3 mo or substance abuse within the past year (based on history taken by study psychiatrist); were pregnant or lactating; history of hypersensitivity, intolerance, or contraindication to NAP/LAN or ESZ; abnormalities on baseline laboratory tests indicating kidney or clotting dysfunction; taking medications that have significant renal effects, anticoagulants, or corticosteroids (in the past 30 days) or any medications known to affect sleep within five half-lives of screening or during the study; allergy to aspirin; history of diagnosed gastric/duodenal ulcer, bleeding or clotting diathesis, myocardial infarction or cerebrovascular accident; history of back-related surgery within 3 mo, back surgery other than discectomy in the past 2 years, or any surgery in the past month; LPB-related pending litigation or workers' compensation claim; inability to follow study procedures or complete the study; child-bearing potential in those who would not agree to use approved means of birth control;

spondyloarthropathy, sciatica or other radicular back pain, spinal stenosis, vertebral fractures, or spondylolisthesis.

Measures

Sleep and Pain Diaries

Self-ratings of sleep and pain were obtained from sleep diaries entered into a personal digital assistant or on paper by subjects each morning throughout the study. These data were used in analyses as baseline and outcome sleep and pain self-rated measures. Pain ratings included a global impression of pain rating (PGI) (1-5 rating) and a VAS pain rating (0-100 scale).[22] Subjects entered the time of lights out, how long it took them to fall asleep, the duration of each period awake in the middle of the night, the time of the final awakening in the morning, and the time of lights on when they got out of bed to start the day. From these data we derived: SOL, wake time after sleep onset (WASO), TST, number of awakenings (NWAK), sleep efficiency (SE%), sleep quality (10-point rating), and the degree of restedness upon arising (10-point scale). TST was calculated as the time from lights out to lights on minus the time it took to fall asleep, and the sum of the time of all of the awakenings throughout the night, including the time from the last awakening until lights on.

The Insomnia Severity Index

The ISI is a seven-item self-report questionnaire that provides a global measure of insomnia severity based on difficulty falling or staying asleep, satisfaction with sleep, or degree of impairment with daytime functioning.[23] The total score ranges from 0–28: 0–7 (no clinical insomnia), 8–14 (subthreshold insomnia), 15–21 (insomnia of moderate severity), and 22–28 (severe insomnia). The ISI has adequate internal consistency (Cronbach alpha = 0.91) and temporal stability (r = 0.80). It has been validated against sleep diary and polysomnography data[24] and was sensitive to change in several insomnia treatment studies.[19,25]

Roland-Morris Low Back Pain Disability Questionnaire

The Roland-Morris Low Back Pain Disability Questionnaire (RMLBPDQ) is a 24-item instrument that assesses the extent to which activities of daily living are affected by LBP.[26] It is composed of 24 "yes-no" items assessing potential disabilities. Scores range from 0 (no disability) to 24 (severe disability). This instrument has been included in a number of trials of the treatment of LBP.[27–29]

Hamilton Depression Rating Scale

The 24-item Hamilton Depression Rating Scale (HAM-D) was administered to assess depression severity in this study. The HAM-D is considered to be a gold standard measure of depressive symptoms with high validity and reliability, and demonstrated sensitivity to change with treatment.[30,31]

Statistical Analysis

All statistical tests used two-tailed tests of significance and used a probability of less than 5% as an indicator of significance. Analyses of outcome variables were analyses of covariance (ANCOVA) carried out with rank-transformed data because of the expected nonnormality of the probability distribution as was carried out in prior randomized, placebo-controlled trials of eszopiclone.[14,19–21] All analyses were carried out with the Last-Observation Carried Forward (LOCF – a.k.a. Intent to Treat or ITT) population to retain the integrity of the randomization using SAS version 9.1 (SAS, Cary, NC). The baseline value of each outcome variable was included as a covariate in analysis. In keeping with the standard LOCF methodology we did not include subjects who did not receive any treatment.[32]

The outcome variables analyzed included:

1. *A priori* specified primary outcome measure: TST.
2. Primary pain measures: VAS pain ratings and PGI of pain severity derived from diaries.
3. Secondary sleep measures – WASO, SOL, SE, awakenings, quality, and restedness as well as the ISI.
4. Secondary pain measures: Clinicians Global Impression (CGI) rating.
5. Assessments of function/depression: the RMLBPDQ, and HAM-D24.

We chose TST as the primary outcome measure because we sought a single sleep measure that would indicate whether ESZ had a therapeutic effect on sleep with the understanding that it would not indicate the nature of that effect. The reason we sought to use a single primary outcome measure is that we knew that our power to detect effects would be limited in this study. TST reflects the combination of both onset and maintenance effects with a single variable.[33,34] Alternatives to TST that have been used in studies of insomnia medications are SOL and WASO. SOL reflects only the ability to fall asleep but not the ability to stay asleep, whereas WASO reflects only the ability to stay asleep but not the ability to fall asleep. Choosing either WASO or SOL runs the risk of having a falsely negative outcome for our study if we had a therapeutic effect only on the aspect of sleep that the variable we chose did not measure. The choice of TST eliminates this risk and provides the desired single measure indicating whether there is a therapeutic effect on some aspect of sleep. We were aware that this would not allow us to determine the relative sizes of effects on onset or maintenance. However, this is in keeping with our primary goal, which was to provide "proof of concept" that it was possible to improve sleep in patients with LBP and insomnia, and that this might be related to improving pain. It was understood that the relative size of sleep onset and maintenance effects would be determined in follow-up analyses carried out with secondary outcome variables (SOL and WASO).

To investigate the sleep-pain relationship, exploratory Spearman correlation analysis of the change from baseline in daily diary ratings of sleep and pain were also carried out. Exploratory analyses of covariance were also carried out to assess the effects of treatment on outcomes over time.

Because there are no prior studies of insomnia treatment in LBP, we estimated the expected effect size for the primary outcome measure (TST) using data from prior placebo-controlled studies of ESZ treatment of primary insomnia and insomnia co-occurring with rheumatoid arthritis.[8,14,35] Our trial was designed to enroll 70 subjects, assuming that 15% would ultimately fail to qualify or drop out before the first outcome assessment, as this would provide more than 80% power to detect the expected effect size at the $\alpha = 0.05$ level in a two-tailed

test of significance.[8,14,35] Although the failure/dropout rate was somewhat higher than expected at 25%, enrolling 70 subjects still provided 80% power to detect the expected effect size.[8,14,35]

No interim analyses were planned or carried out, and there were no changes to trial methods or outcomes after the trial commenced.

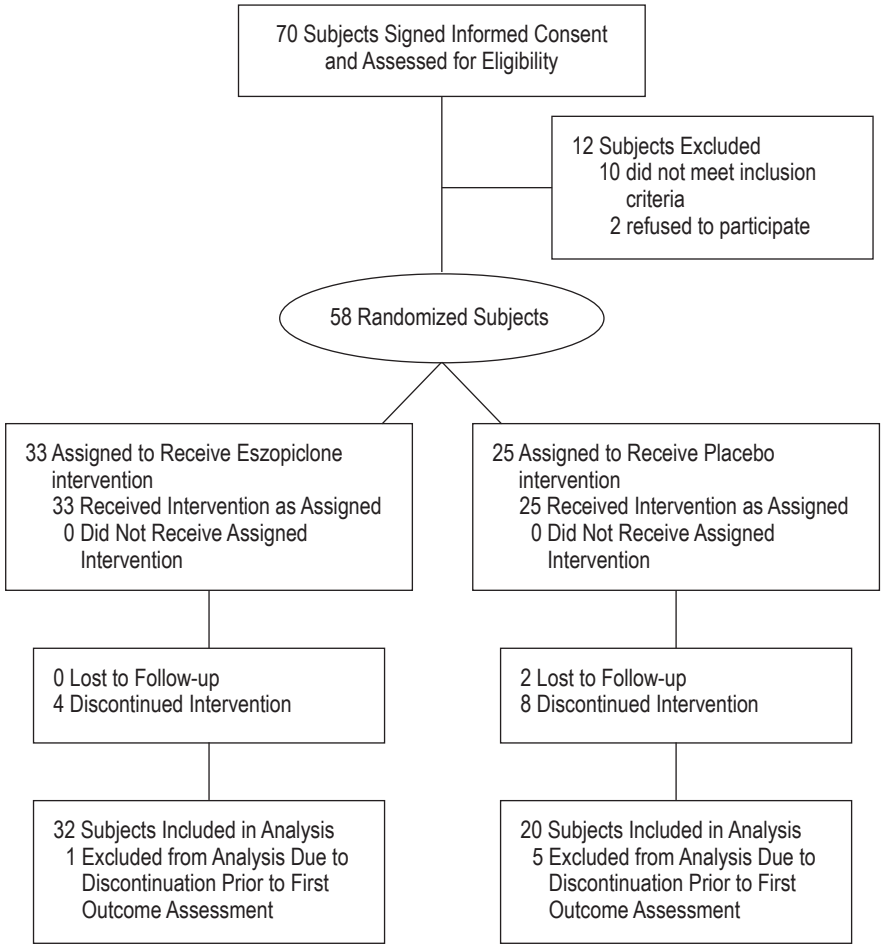

Figure 1—Subject flow diagram.

Table 1—Demographic characteristics of the study subjects

	Eszopiclone subjects (n = 32)	Placebo subjects (n = 20)
Mean age (SD)	45.7 (11.0)	40.1 (12.8)
Sex (% female)	59.4	70.0
Race/Ethnicity		
% African American	43.8	50.0
% Caucasian	43.8	45.0
% Other	12.4	5.0
Mean Hamilton Depression Rating Scale Score (SD)	6.5 (2.3)	7.1 (2.8)
Mean Insomnia Severity Index Score (SD)	18.9 (4.0)	20.3 (4.1)
Mean Clinical Global Impression of Pain Severity Rating (SD)	4.3 (0.6)	4.3 (0.5)
Mean Roland Morris Low Back Pain Inventory Score (SD)	12.3 (5.7)	11.3 (5.7)

SD, standard deviation.

RESULTS

Study Population

Seventy participants were enrolled (Figure 1). Of these, 12 ultimately failed to meet study inclusion criteria or dropped out prior to randomization. Of the 58 randomized subjects, 44 (76%) completed double-blind treatment. Of the 14 subjects (24%) who discontinued the study, six (10%) discontinued after randomization, but before receiving a dose of double-blind study drug. As a result, these six subjects were not included in efficacy or safety analyses. These six subjects discontinued participation in the study because of: inability to tolerate naproxen (n = 1); inability to follow study procedures (missing appointments and failing to take study medication) (n = 2); and failure to return without giving reason and without responding to repeated phone calls (n = 3). The 52 subjects who were randomized and returned for at least one postrandomization assessment represent the evaluable subjects that comprised the study sample.

Demographics of the subjects randomized to ESZ and placebo are shown in Table 1 and did not significantly differ between the treatment groups. It should be noted that subjects did not have comorbid medical or psychiatric conditions or concomitant medications having significant renal effects, anticoagulants, or corticosteroids (in past 30 days) or any medications known to affect sleep within five half-lives of screening or during the study because these were exclusion criteria for this study. Baseline values in outcome variables did not differ between groups (Tables 2 and 3) except for TST, where the placebo group had significantly longer TST. The eight subjects (14%) who discontinued during the double-blind treatment phase of the study included five subjects randomized to placebo and three subjects randomized to receive ESZ. The reasons for discontinuation among the subjects randomized to placebo were: failure to return without giving reason and without responding to repeated phone calls (n = 2); non-adherence to the study protocol (n = 2); and transportation difficulties (n = 1). The reasons for discontinuation among the subjects randomized to ESZ were: non-adherence to the study protocol (n = 1); moved out of the region (n = 1); and started a new job (n = 1).

Outcome Analyses

ESZ led to significantly greater improvement than placebo in the primary

outcome variable, TST ($P < 0.001$). For the primary pain outcomes, there was a significant effect for VAS pain ($P < 0.004$), although a significant PGI pain effect was not found ($P < 0.08$; Tables 2 through 4).

Significantly greater improvement in all other sleep measures was seen with ESZ compared with placebo except for restedness ratings. No significant effect versus placebo was seen for CGI ratings of pain. ESZ was also associated with improvements in depression severity ($P < 0.024$) compared with placebo.

Follow-up exploratory ANCOVA, carried out to assess the effects of treatment over time (Table 3), indicated that significant treatment effects on sleep were evident from the beginning of double-blind treatment, whereas significant pain and depression effects increased substantially over the double-blind treatment period. Significantly lower PGI pain ratings were seen with ESZ at w 2 ($P < 0.03$) and 4 ($P < 0.05$), and we observed significantly lower HAM-D24 scores only at w 4 ($P < 0.002$).

Table 2—*A priori* specified outcome analyses: analysis of variance on ranked difference from baseline to final double-blind treatment value

Variable	F	P
Primary outcome analysis		
Total sleep time	23.44	0.0001
Secondary sleep outcome analysis		
Sleep onset latency	6.16	0.017
Wake time after sleep onset	10.37	0.0024
Sleep efficiency	33.95	0.0001
Number of awakenings	7.34	0.0094
Quality ratings	5.60	0.022
Restedness ratings	2.98	0.091
Insomnia Severity Index score	4.82	0.033
Pain outcome analysis		
Visual analog scale of pain (diaries)	9.05	0.004
Patient Global Impression of Pain (diaries)	3.20	0.080
Clinical Global Impression of Pain	1.70	0.20
Function outcomes		
Hamilton Rating Scale for Depression	5.50	0.024
Roland Morris Low Back Pain Inventory Score	3.20	0.08

Relationship Between Sleep and Pain Outcomes

We found that greater improvement in nearly all of the sleep variables was significantly associated with greater improvement in VAS and PGI pain ratings (Table 5).

Safety

There were no serious adverse events during the study. Three adverse events occurred during double-blind treatment and none led to discontinuation. They consisted of two events occurring in the ESZ group (headache and noncardiac chest pain) and one event in the placebo group (headache). All three were rated as moderate in severity and resolved without intervention.

DISCUSSION

This is the first study to evaluate the treatment of insomnia, specifically in patients with LBP in a placebo-controlled trial. It is also the first study of the treatment of insomnia occurring in pain patients where all subjects were placed on a standardized pain medication treatment regimen. The findings suggest that adding ESZ to pain therapy significantly improves sleep and that this change may be associated with improved pain and less depression.

The findings are consistent with a previous rheumatoid arthritis study where ESZ significantly improved sleep and some pain ratings compared with placebo.[7] Additional studies in other pain populations will be needed to determine the extent to which the observed therapeutic effects are linked to the treatment of insomnia associated with pain in general or are just seen in these specific pain conditions

Although several earlier studies of insomnia treatment in pain populations did not find clear indications of a therapeutic effect on sleep and/or pain, this may reflect that these smaller studies were likely underpowered, and, in some cases, used less rigorous control interventions.[7,9–12] Another possibility is that the therapeutic pain effects seen in the current study are specific to ESZ and not associated with all effective insomnia therapies. This type of specificity has been observed with the treatment of insomnia occurring with major depression and generalized anxiety disorder, where ESZ improved sleep and the severity of the comorbid conditions, whereas zolpidem extended-release only improved sleep.[15,17,18,36,37] Studies of insomnia treatment in LBP with other insomnia interventions will be needed to resolve this question.

The identified correlations between improvement in sleep and improvement in pain indicate that improving sleep disturbance may contribute to improvement in pain severity. However, it is important to note that changes in sleep accounted for only a modest amount of the variance in pain ratings. Nonetheless, this trial provides the best evidence to date supporting the emerging model that insomnia has important and independent effects on the clinical course of pain conditions. Targeting treatment to both insomnia and pain complaints appears to have the potential to improve outcomes compared with administering pain therapy alone.[5,6]

Limitations

(1) We obtained only self-reported sleep outcomes. Although these measures define the insomnia syndrome and are the basis for clinical management of insomnia, polysomnographic data would be helpful to provide objective confirmation that significant therapeutic sleep effects occurred with ESZ versus placebo. (2) The period of double-blind treatment was relatively short. The data suggest that differences between ESZ and PBO on pain and depression ratings were increasing with time, so it would be of interest to study a longer period of therapy to determine if greater pain effects occur. In this regard, unlike pain, the sleep effects of treatment were maximal from the beginning of double-blind therapy as is typically seen in studies of insomnia pharmacotherapy. This suggests some dissociation of the improvement in sleep and improvements in pain and mood. This replicates HAM-D24 findings of a prior placebo-controlled study of ESZ in those with insomnia and comorbid depression.[15] Although the reason for the dissociation is unknown, one possibility is that sleep needs to be improved for some time before it results in improvement in comorbid pain and mood difficulties. (3) As part of a standardized pain

Table 3—Treatment effects over time

	Eszopiclone 3 mg (n = 32)		Placebo (n = 20)		P value[a]	
	Median	Mean (SD)	Median	Mean (SD)	ESZ vs PBO	Effect size[b]
Sleep Measures						
Total sleep time (min)						
Postnaprosyn baseline[c]	326.00	316.96 (91.55)	399.25	380.45 (81.33)	0.02	–
Week 1	409.00	403.47 (77.67)	379.38	375.56 (88.74)	0.0001	0.9
Week 2	411.00	421.97 (68.28)	380.50	382.11 (96.13)	0.0001	0.97
Week 4	405.81	411.97 (66.87)	376.19	388.96 (99.02)	0.017	0.67
Sleep onset latency (min)						
Postnaprosyn baseline	33.31	38.28 (23.90)	24.25	34.11 (25.93)	0.56	–
Week 1	17.14	22.36 (16.59)	18.50	27.00 (18.28)	0.025	0.60
Week 2	14.29	17.50 (12.33)	16.78	23.10 (19.68)	0.078	0.46
Week 4	14.00	15.28 (12.95)	17.54	19.91 (12.30)	0.026	0.60
Wake time after sleep onset (min)						
Postnaprosyn baseline	86.71	91.51 (55.91)	72.00	81.43 (54.58)	0.53	–
Week 1	40.14	49.34 (32.62)	50.75	76.71 (65.84)	0.012	0.69
Week 2	32.43	37.07 (22.21)	54.63	81.32 (76.30)	0.0001	0.85
Week 4	33.33	36.74 (28.44)	62.50	76.18 (65.50)	0.0009	0.82
Sleep efficiency (%)						
Postnaprosyn baseline	70.42	69.91 (14.58)	79.50	76.61 (12.36)	0.10	–
Week 1	84.88	84.44 (8.44)	82.09	78.03 (13.67)	0.0001	1.04
Week 2	88.75	88.15 (5.75)	83.31	78.76 (15.63)	0.0001	1.21
Week 4	87.75	88.41 (6.68)	81.60	79.21 (14.30)	0.0004	0.88
Number of awakenings						
Postnaprosyn baseline	2.07	2.29 (1.48)	1.79	2.08 (1.51)	0.62	–
Week 1	1.08	1.31 (1.02)	1.45	1.98 (1.43)	0.002	0.74
Week 2	1.14	1.35 (0.99)	1.44	2.13 (1.81)	0.004	0.71
Week 4	1.29	1.33 (1.01)	1.89	2.34 (1.79)	0.021	0.61
Sleep quality ratings (1-10 Likert scale)						
Postnaprosyn baseline	4.75	4.52 (1.45)	4.22	4.44 (1.66)	0.86	–
Week 1	5.50	5.99 (1.43)	5.05	4.90 (1.83)	0.017	0.68
Week 2	6.00	6.18 (1.45)	5.06	5.33 (1.77)	0.046	0.54
Week 4	6.16	6.38 (1.66)	4.95	5.29 (2.00)	0.035	0.62
Morning restedness ratings (1-10 Likert scale)						
Postnaprosyn baseline	4.78	4.71 (1.38)	3.93	4.16 (1.80)	0.23	–
Week 1	5.60	5.79 (1.36)	5.00	4.81 (1.85)	0.12	0.40
Week 2	6.00	6.11 (1.39)	5.38	5.27 (1.98)	0.21	0.35
Week 4	6.17	6.24 (1.64)	5.1	5.21 (1.96)	0.12	0.41
ISI						
Prenaprosyn baseline	18.00	18.85 (4.01)	20.00	20.26 (4.07)	0.20	–
Postnaprosyn baseline	18.00	18.00 (3.41)	16.00	16.78 (4.32)	0.24	–
Week 1	11.50	11.28 (6.10)	11.50	12.85 (5.97)	0.073	0.47
Week 2	11.00	10.61 (6.60)	12.00	12.74 (6.39)	0.056	0.51
Week 4	7.00	8.38 (6.42)	15.00	13.75 (6.78)	0.001	0.75
Pain Measures						
Visual analog scale pain ratings						
Postnaprosyn baseline	52.00	48.51 (16.22)	53.00	53.79 (20.96)	0.33	–
Week 1	44.00	40.72 (17.13)	50.40	51.99 (20.83)	0.038	0.63
Week 2	36.00	34.70 (18.49)	50.00	51.25 (19.61)	0.013	0.69
Week 4	33.61	31.69 (17.92)	50.00	51.60 (22.44)	0.003	0.72
Patient Global Impression of Pain Ratings						
Postnaprosyn baseline	4.05	4.02 (0.95)	4.19	3.90 (1.47)	0.73	–
Week 1	3.60	3.54 (1.17)	3.90	3.82 (1.45)	0.155	0.38
Week 2	3.40	3.30 (1.27)	4.00	4.01 (1.12)	0.033	0.61
Week 4	3.20	3.08 (1.28)	3.54	3.80 (1.14)	0.05	0.48
CGI						
Prenaprosyn baseline	4.00	4.27 (0.63)	4.00	4.30 (0.47)	0.84	–
Postnaprosyn baseline	4.00	3.88 (0.66)	4.00	3.91 (0.67)	0.82	–
Week 1	4.00	3.39 (0.95)	3.50	3.35 (0.93)	0.85	0.00
Week 2	3.00	3.25 (1.00)	3.00	3.37 (0.83)	0.77	0.10
Week 4	3.00	2.67 (1.33)	3.00	3.31 (1.01)	0.08	0.45
RMLBPI						
Prenaprosyn baseline	13.5	12.27 (5.70)	11.00	11.33 (5.66)	0.57	–
Postnaprosyn baseline	11.00	9.97 (5.55)	9.00	10.30 (5.75)	0.83	–
Week 1	7.00	9.10 (6.37)	7.50	9.05 (6.32)	0.21	0.35
Week 2	5.00	7.63 (6.34)	7.00	9.32 (6.25)	0.44	0.21
Week 4	6.00	6.59 (5.49)	5.50	7.94 (6.99)	0.46	0.20
Depression Measures						
HAMD-24						
Prenaprosyn baseline	6.0	6.45 (2.26)	6.0	7.10 (3.83)	–	–
Postnaprosyn baseline	7.0	6.38 (2.37)	6.0	6.57 (3.63)	–	–
Week 1	4.0	4.54 (3.71)	4.5	5.53 (3.28)	0.20	0.35
Week 2	3.0	4.14 (3.50)	4.0	5.07 (3.61)	0.29	0.33
Week 4	2.0	2.62 (2.61)	5.0	6.21 (5.18)	0.002	0.74

[a]Statistical testing involved analysis of covariance comparing values at each time point for eszopiclone (ESZ) vs placebo (PBO) groups where baseline values served as covariates; [b]Effect size was determined as the group difference in least-squared means (adjusted for baseline) divided by the pooled standard deviation (SD); [c]Diary data were not collected prior to naprosyn administration so prenaprosyn baseline values are only available for the Insomnia Severity Index (ISI), Clinical Global Impression of Pain (CGI), Roland Morris Low Back Pain Inventory (RMLBPI), and Hamilton Depression Rating Scale Score (HAMD-24).

regimen, we excluded all subjects who might have required opioid therapy to manage their pain because it limits study generalizability. (4) Subjects were selected based on specific criteria that may also limit generalizability (insomnia did not predate LBP onset by more than 1 mo; subjects reported usual nightly TST less than 6.5 h and/or usual SOL more than 30 min for the month prior to screening; ISI greater than14). (5) Although all subjects were required to have LBP for more than 3 mo, we did not collect data on the duration of LBP and, as a result, we could not provide these data as an indication of the nature of the study sample, nor could we include duration of LBP in data analyses. (6) We used TST as a single primary outcome measure because of power limitations. This prevented us from being able to determine with *a priori* specified primary outcome measures the extent to that adding ESZ to NAP therapy improves sleep onset versus sleep maintenance in patients with LBP. Future studies will be needed to determine if the findings of the current study are generalized to patients with LBP taking opiate therapy and those who would not meet the specific entry criteria of this study. Despite these limitations, this study supports the importance of treating insomnia in those with LBP and provides the best evidence to date that treating sleep disturbance may improve pain severity.

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Table 4—Spearman correlation analysis of the relationship of the change in diary-derived sleep and pain ratings with treatment

Sleep Variable	r VAS pain rating	r PGI pain rating
Total sleep time	-0.40 [c]	-0.46 [c]
Sleep onset latency	-0.05	-0.04
Wake time after sleep onset	0.31 [b]	0.32 [b]
Number of awakenings	0.38 [c]	0.25 [a]
Sleep efficiency	-0.33 [b]	-0.33 [b]
Sleep quality	-0.37 [c]	-0.27 [a]
Restedness	-0.41 [c]	-0.33 [b]

[a] $P < 0.10$; [b] $P < 0.05$; [c] $P < 0.01$. VAS, visual analog scale; PGI, Patient Global Impression.

Sunovion Corporation (then Sepracor Corporation) to Dr. Krystal. Sunovion also provided matching eszopiclone 3 mg and placebo capsules. Sunovion provided funding and medications for the trial and generated the randomization sequence and provided sequentially numbered pill containers in order to implement the random allocation sequence and ensure that all of the investigators and study personnel were blinded to treatment allocation during the trial. Dr. Krystal has received research support from NIH, Sanofi-Aventis, Cephalon, Glaxo-SmithKline, Merck, Neurocrine, Pfizer, Sunovion/Sepracor, Somaxon, Takeda, Transcept, Phillips-Respironics, Neurogen, Evotec, Kingsdown Inc., Astellas, and Abbott; he has consulted for Abbott, Actelion, Arena, Astellas, Axiom, AstraZeneca, BMS, Cephalon, Eisai, Eli Lilly, GlaxoSmithKline, Jazz, Johnson and Johnson, King, Merck, Neurocrine, Neurogen, Novartis, Organon, Ortho-McNeil-Janssen, Pfizer, Respironics, Roche, Sanofi-Aventis, Somnus, Sunovion/Sepracor, Somaxon, Takeda, Transcept, and Kingsdown Inc. The other authors have indicated no financial conflicts of interest.

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