

Project proposal

Lead Researcher Name: Marcel Hungs, MD, PhD

Study Title: Double blind, placebo controlled, crossover trial on the effect of Optically Modified Polyethylene Terephthalate Fiber mattress covers on sleep disturbances in patients with chronic back pain

A. NON-TECHNICAL SUMMARY

Celliant™ is a commercially available polymer fabric constructed from polyethylene terephthalate (PET) yarn containing optically active particles – a proprietary mixture of natural and inorganic materials – which scatter and reflect visible and near infrared light. Garments constructed with such optically modified fibers are thought to influence transmission and reflectance of electromagnetic energy into underlying tissue and skin. Numerous anecdotal reports from patients with a variety of chronic pain syndromes indicate that wearing Celliant™ garments for even a few days leads to dramatic improvement or complete resolution in subjective pain. A recent report of Celliant™ socks ameliorate chronic pain resulting from diabetic neuropathy and other disorders of the foot (York & Gordon see attachment).

This double-blind, crossover, placebo controlled study will evaluate whether a mattress cover made from polyethylene terephthalate (PET) incorporating optically active particles (Celliant™) ameliorate sleep disturbances in patients with chronic back pain using sleep / pain questionnaires as well as actigraphy data as outcome measures.

B. PURPOSE AND BACKGROUND OF THE RESEARCH

This double blind, placebo controlled, crossover trial will evaluate the effect of Optically Modified Polyethylene Terephthalate Fiber mattress covers (OMPETFMC) on sleep disturbances in patients with chronic back pain

1. Primary Hypothesis

OMPETFMC improves sleep quality in patients with lower back pain as measured by Clinical Global Impression (CGI).

2. Secondary Objectives

OMPETFMC improves sleep variables measured with actigraphy in patients with lower back pain

- a. Sleep parameters measured by actigraphy include:
 - i. Nighttime Wake-time After Sleep Onset (nWASO)
 - ii. Wake-Time During the Sleep Interval (WTDS)
 - iii. Number of Nighttime Awakenings (nNAW)
 - iv. Daytime Total Sleep Time (dTST)
 - v. Ratio of Daytime to Nighttime Sleep (dTST: nTST)
 - vi. Number of Daytime Naps
 - vii. Sleep Efficiency (SE)
- b. Safety and tolerability (via AE, PE, vital signs)

3. Exploratory Objectives

- a. Sleep Disorders Inventory (SDI)
- b. Pittsburgh Sleep Quality Index
- c. Visual analogue scale for pain

Background and literature review:

1. The relationship of nocturnal pain and sleep

Animal experiments and studies in humans show that the relation between pain and sleep quality is two-way: sleep disorders can increase pain, which in turn may cause sleep disorders. Sleep disorders and chronic low back pain are frequent health problems and it is unsurprising that the two can co-exist¹. Nociceptive information is essential to survival; when perceived by the organism as pain, defensive mechanisms are recruited to protect the organism from further damage. Pain can interfere with sleep. Sleep serves numerous functions. Although the exact nature of these functions is still not clear, any persistent deprivation or fragmentation of sleep increases the homeostatic sleep drive, inevitably producing a rapid sleep onset. Sleep cannot be avoided when the homeostatic sleep drive reaches its maximum; sleep intrudes into wakefulness in the form of brief microsleeps, resulting in automobile and workplace accidents. When these two vital functions, pain and sleep, interact, the biological and behavioral capacity of the individual is compromised².

The literature describing the sleep of patients experiencing chronic pain is more extensive than that of acute pain, but also less definitive. The diseases studied are diverse and include the various headache disorders and the peripheral neuropathies with associated pain such as diabetic neuropathy and postherpetic neuralgia. Sleep and fatigue in musculoskeletal diseases, including rheumatoid arthritis, osteoarthritis, and fibromyalgia, have also been studied, as have conditions in which pain is diffuse, nonspecific, and not related to structural pathology (e.g., chronic fatigue syndrome)².

Acute and chronic pain are associated with disturbed sleep. However, to date the specific nature of the sleep disturbance, its causal mechanisms, and its effective treatment have not been thoroughly explored. In chronic pain, the specific nature of the sleep disturbance and its pathological significance is not as clear. In part, the problem relates to the complexity and heterogeneity of the chronic pain conditions and their comorbidity with psychiatric conditions, typically depression and anxiety. Experimental models of the sleep-pain interaction have shown that the relation is bidirectional. In healthy, pain-free subjects sleep has an antinociceptive effect and the loss of sleep has a hyperalgesic effect².

A prospective cross-sectional survey of 268 patients 18 yrs or older using a 43-item composite form that contained the Short-Form McGill Pain Questionnaire (SF-MPQ); the Pittsburgh Sleep Quality Index (PSQI); a pain visual analog scale (VAS); and questions regarding bed type, sleep position, and patients' sleep description found that chronic low back pain significantly affects quality of sleep and that sleep problems should be addressed as an integral part of the pain management plan³.

Not surprisingly, Menefee et al. showed that higher overall sleep quality and lower sleep latency were primarily related to higher ratings of physical functioning and shorter duration of pain⁴. His data suggests that physical functioning, duration of pain, and age may be more important than pain intensity and depressed mood in contributing to decreased overall sleep quality and sleep latency⁴. The contribution of physical functioning was particularly strong and should be included in subsequent studies of sleep, pain, and mood.⁴

2. Sleep and mattress research

It is commonly observed that sleep in its quantity and quality is influenced by the type of mattress used at night. A recent randomized, single-blinded, parallel-group study evaluated 3 structurally different mattresses relative influence on patients with chronic low back pain (CLBP) revealing that the Waterbed and foam mattress' did influence back symptoms, function and sleep more positively than did the hard mattress⁵.

Another study compared sleep comfort and quality between personal and new bedding systems. Subjects recorded back and shoulder pain, sleep quality, comfort, and efficiency for 28 days each in their personal

beds (pre) and in new medium-firm bedding systems (post). It was concluded that new tested bedding systems can significantly improve selected sleep variables and that continuous sleep quality may be dependent on timely replacement of bedding systems⁶.

Another study suggests that subjects obtain significant improvement in shoulder and back pain, back stiffness, and quality of sleep after 28 days of prescribed bedding system use as compared with 28 days of personal bedding use⁷. Female subjects and those with lower body weight were more likely to significantly improve than heavier and more obese subjects⁷.

SF-36 and VAS outcomes measures show highly significant benefit for airbeds. The airbed appears to be a useful sleep aid and an adjunct to medical and physical therapies for chronic back pain sufferers compared to regular innerspring mattresses⁸.

3. **What is polyethylene terephthalate (PET)^A?**

Polyethylene terephthalate [sometimes written poly(ethylene terephthalate), commonly abbreviated PET, PETE, or the obsolete PETP or PET-P], is a thermoplastic polymer resin of the polyester family and is used in synthetic fibers; beverage, food and other liquid containers; thermoforming applications; and engineering resins often in combination with glass fiber. It is one of the most important raw materials used in man-made fibers. It is a commonly used product in the US.

The majority of the world's PET production is for synthetic fibers (in excess of 60%) with bottle production accounting for around 30% of global demand. In discussing textile applications, PET is generally referred to as simply "polyester" while "PET" is used most often to refer to packaging applications. The polyester industry makes up about 18% of world polymer production and is third after polyethylene (PE) and polypropylene (PP).

4. **Mechanism of CelliantTM**

The mechanism how optically modified fiber garments improve sleep associated with nocturnal pain is unclear. The patent for the Celliant garments is attached as Attachment B. Two unpublished studies^B, one in healthy subjects and one in diabetics, demonstrated significant increases in transcutaneous oxygen tensions in the skin of the hands and feet when CelliantTM garments were worn compared to placebo garments. The increased oxygen tensions were observed by 10 minutes and persisted during repeated measurements over 60 minutes. The increase in healthy subjects ranged from 10 to 24%; diabetic subjects showed an average increase of 10%. It is conceivable that some interaction of the CelliantTM particles with light increases reflection or transmission of light in the visible or near infrared portion of the spectrum into the skin, leading to vasodilation of the microcirculation and enhanced perfusion of tissue, which plausibly could ameliorate some causes of chronic pain. Alternatively, the enhanced illumination of the skin and underlying tissues could influence the biologic activity of endogenous chromophores (cytochromes, flavins, and porphyrins) involved in energy metabolism in a manner leading to anti-inflammatory or anti-nociceptive effects.

A large body of evidence suggests that short periods of illuminating skin, tissue, and cells with visible or infrared light has positive effects on pain, injury recovery, and wound healing. A number of studies have looked at joint pain such as temporomandibular joint pain, finding that near infrared light (810 nm) appears to reduce pain compared to sham illumination regimens⁹. A meta-analysis of 20 trials employing laser therapy for chronic joint disorders found that when sufficiently intense light was employed, such

^A http://en.wikipedia.org/wiki/Polyethylene_terephthalate

^B Information provided by Hologenix, LLC.

- Lavery LA. Improving blood flow with Holofiber in the hands and feet of high-risk diabetics. Unpublished observations, 2003
- McClue GM, Lavery LA. Holofiber study of thirteen healthy subjects. Unpublished observations, 2003

therapy had a direct anti-inflammatory effect on the joint capsule¹⁰. A study of the effects of infrared (950 nm) on sural nerve conduction showed significant impact of illumination on nerve conduction velocity and negative peak latency compared to sham illumination¹¹. Low intensity laser therapy at 810-820 nm combined with exercise regimens has been shown to benefit patients with chronic back pain and Achilles tendonopathy^{12, 13}. Several studies using animal models of wound healing or cell cultures have examined the effects of short exposures to red (e.g., 632nm, 670 nm) or infrared light (e.g., 830 nm), finding wound healing to be significantly accelerated or increased expression of genes and proteins associated with proliferation¹⁴⁻¹⁷.

A study at the VA Long Beach suggests that Celliant™ fabric socks lead to a reduction in pain associated with chronic foot disorders^C.

Future studies looking at other chronic pain conditions such as carpal tunnel syndrome and knee arthropathies are planned as well as attempts to elucidate the mechanism by examining the influence of the modified garments on tissue perfusion, temperature, oxygen levels, and inflammation.

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^C Robyn M. Burgess York RM, Gordon IL: Effect of Optically Modified Polyethylene Terephthalate Fiber Socks on Chronic Foot Pain (manuscript in preparation) see Attachment A

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C. ROLES AND EXPERTISE OF THE STUDY TEAM

Lead Researcher:

Marcel Hungs, MD, PhD is Assistant Professor of Clinical Neurology and Director of the Center for Sleep Medicine at the University of California, Irvine. He is board certified in both Neurology and Sleep Medicine. He is Vice-Chair of the UC Irvine IRB biomedical committee (B).

Dr. Hungs received his M.D. and Ph.D. from the University of Aachen Medical School in Aachen (Germany) in 1995. He did his Neurology residency training in Germany at the University of Aachen and here at UC Irvine. He completed prestigious Sleep Disorders Medicine research fellowship training at Stanford University. He has over 15 years of experience on all aspects of clinical Sleep Medicine. His academic work has a focus in Narcolepsy. Dr. Hungs authored and coauthored over 60 publications, reviews, book chapters and abstracts. Among other accomplishments, he contributed to the discovery of the involvement of Hypocretin/Orexin System in sleep and in human and canine Narcolepsy.

Dr. Hungs will be the lead researcher for this project at the University of California, Irvine. Dr. Hungs is responsible for the conduct of the trial and adherence to all obligations of an investigator at UC Irvine. He will be involved in all aspects of the study, including, but not limited to, determining subject eligibility, consenting subjects, interpreting subject identifiable data, collecting data for medical files, and answering questions about the study.

Research Personnel:

The following Research Personnel is staff of the Center for Sleep Medicine and may be involved in explaining the study to the subjects, collecting data for research and medical files, completing adverse events and progress reports, reporting protocol violations, and answering questions about the study:

Tillie Davis

The following Research Personnel is staff of the Center for Sleep Medicine and may be involved in performing the actigraphy, explaining the study to the subjects, collecting data for research and medical files, completing adverse events and progress reports, reporting protocol violations, and answering questions about the study:

Amalia Rodriguez
Jackie Halte
Gloria Rodriguez
Selvia Alaga-Leaea

D. RESEARCH METHODOLOGY/STUDY PROCEDURES

This is a double-blind, randomized, crossover, placebo-controlled study to evaluate the effect of Optically Modified Polyethylene Terephthalate Fiber mattress covers (OMPETFMC) on sleep disturbances in patients with chronic back pain.

The total duration of the study will be approximately 42 days, including 14 days of screening and 28 days of treatment. There will be initial subject screening, which will include medical history (including assessing severity of lower back pain and sleep history), physical examination and medical record review for each subject. Subjects who meet the initial screening criteria will then undergo actigraphy monitoring for a period of 14 days to record a baseline sleep pattern. Subjects will be offered in this crossover double blind designed trial either the active or the placebo garment mattress cover. 14 day actigraphy with use of the provided study material is performed followed by the crossover offering of the appropriate garment for the next 14 days.

1st Screening Visit and initiating of baseline sleep assessment (Visit 1)

Subjects will be screened for enrollment at the first Screening (Visit 1 and Day -14, relative to randomization). Subjects will be screened in accordance with the inclusion/exclusion criteria that are detailed in section 4 below. The following procedures will be completed at Screening (Visit 1):

1. Informed Consent process and document.
2. Confirm clinical diagnosis of lower back pain
3. Obtain subject's medical history, demographic information, sleep history, prior medication history, concurrent medical conditions, and concomitant medication.
4. Perform vital signs, height, weight and a physical examination.
5. Conduct the Sleep Disorders Inventory.
6. Provide actigraphy monitor to be administered and worn throughout the 2-week screening period.
7. Instruct subject on the following:
 - a. Actigraphy procedures and requirements, completion of the sleep log on a daily basis, study compliance
 - b. Daily sleep log recordings (see Attachment C)
 - c. Daily visual analogue pain scale
 - d. Instruct subject to return to the clinic for the 2nd Visit (Visit 2) for the collection of the baseline actigraphy data and sleep log.

Randomization Day (Visit 2)

Randomization will take place on Day 1 (Visit 2) following receipt of actigraphy data from the prior 14 days. The following procedures will be performed and documented during Randomization:

1. Subjects who have met all inclusion (including required actigraphy criteria and pain measured on the visual analogue scale) and none of the exclusion criteria will be randomized during this visit one of two treatments: Active garment mattress cover or placebo garment mattress to be used for the next 14 days in the first part of this study.
2. The following additional procedures and assessments will be performed:
 - a. Vital signs
 - b. Physical exam
 - c. Concomitant medications
 - d. Sleep Disorders Inventory (SDI)
 - e. Clinical Global Impression (CGI) for sleep
 - f. Pittsburgh Sleep Quality Index
 - g. Provide Caregiver Global Impression of Change for Sleep (CGGI) with stamped return mail envelope
 - h. Visual analogue scale analysis
 - i. Following completion of the Randomization Visit procedures, subjects will be instructed to use the mattress cover nightly for the next 14 days
 - j. The study staff will review requirements for completion of the sleep log on a daily basis
 - k. AE(s) and any medication used during the last 14 days are recorded

- l. Provide actigraphy monitor to be administered and worn throughout the 2-week period
- m. Instruct subject on the following:
 - i. Actigraphy procedures and requirements, completion of the sleep log on a daily basis, study compliance (see Attachment C)
 - ii. Daily visual analogue pain scale
 - iii. Instruct subject to return to the clinic for the 3rd Visit (Visit 3) for the collection of the actigraphy data, sleep log and VAS data.

Follow up visit and second step of the randomization (Visit 3)

The following procedures will be performed:

1. Subjects will receive either active garment mattress cover or placebo garment mattress to be used for the next 14 days in the second part of this study.
2. The following additional procedures and assessments will be performed:
 - n. Vital signs
 - o. Physical exam
 - p. Concomitant medications
 - q. Sleep Disorders Inventory (SDI)
 - r. Pittsburgh Sleep Quality Index
 - s. Provide Caregiver Global Impression of Change for Sleep (CGGI) with stamped return mail envelope
 - t. Clinical Global Impression (CGI) for sleep,
 - u. Subjects will be instructed to use the mattress cover nightly for the next 14 days.
 - v. The study staff will review requirements for completion of the sleep log on a daily basis.
 - w. AE(s) and any medication used during the last 14 days are recorded.
 - x. Provide actigraphy monitor to be administered and worn throughout the 2-week period.
 - y. Instruct subject on the following:
 - i. Actigraphy procedures and requirements, completion of the sleep log on a daily basis, study compliance (see Attachment C)
 - ii. Daily visual analogue pain scale
 - iii. Instruct subject to return to the clinic for the 4th Visit (Visit 4) for the collection of the actigraphy data, sleep log and VAS data.

Final Visit (Visit 4) or Early Termination

The Final Visit will be performed at Week 3 or at the Early Termination Visit. The following procedures will be performed and documented:

- Physical examination (capture clinically significant changes from the baseline exam)
- Vital signs
- Weight
- Concomitant medication assessment
- Mattress cover compliance check
- AE assessment
- Sleep Disorders Inventory (SDI)
- Clinical Global Impression (CGI) for Sleep (investigator)
- Sleep Disorders Inventory
- Provide Caregiver Global Impression of Change for Sleep (CGGI) with stamped return mail envelope
- Review Sleep Log and VAS data
- Download Actigraphy Data/Sleep log and send to central scoring site

Early termination may be performed by the study doctor, without subject consent, for any of the following reasons: (a) the Sponsor cancels the study, (b) the study doctor feels it is in the subject's best interest, (c) additional medication is needed by the subject that would interfere with the study, or (d) the subject violates the study requirements or is uncooperative.

Should the subject decide to withdraw them from participation in the study, the following steps must be taken: (a) the subject must notify the study doctor, (b) the subject must bring the subject to the study doctor for a final examination within 72 hours after discontinuing the study medication, and (c) the subject must return all study materials including actigraphy device.

Day	enrollment visit -14	Follow up visit 1	Follow up visit 14	Close out visit 28
Consent	x			
H&P	x			
Vitals	x	x	x	x
Review of Medical History	x			
Teaching Actigraphy use	x	x	x	x
Instruction regarding sleep log	x	x	x	x
Sleep questionnaires	x	x	x	x
Celiant mattress cover		A*	B*	
control mattress		B*	A*	
follow up sleep history		x	x	x
Actigraphy recording		x	x	x
Interval medical history		x	x	x

A*, B*: Participants are enrolled in cross over trial. They are randomized to either the placebo garment or the Celiant garment.

E. SUBJECTS AND INCLUSION/EXCLUSION CRITERIA

1. Number of Subjects screened

40

2. Target sample size

25

3. Inclusion criteria:

1. Clinical diagnosis of chronic lower back pain
2. Pain measured on the Visual Analogue scale
3. The subject has sleep disturbances at night associated with his chronic lower back pain
4. The subject is aged 18 years or older.
5. The subject signs the written, informed consent form prior to the initiation of any study procedures.
6. The subject has an habitual bedtime of between 8 PM and 12 AM.

4. Exclusion criteria:

1. The subject is unwilling or unable to comply with the protocol or scheduled appointments.
2. Subject is unable to understand the language in which the approved informed consent is written.
3. No pain measured on the Visual Analogue scale
4. The subject is non-ambulatory, wheel chair bound or confined to bed
5. The subject is deemed by the investigator to be unreliable to wear the actigraphy, to complete the sleep log, to use the provided mattress covers at the proper time, to come to the scheduled visits or to answer questions regarding the subject's condition or medication use.
6. The subject lacks a mobile upper extremity to which to attach an actigraphy.
7. The subject is currently participating or has participated in another clinical study within the past 30 days.
8. The subject demonstrates an unwillingness to comply with the maximum limit of two alcoholic drinks per day and only 1 alcoholic drink after 6:00 PM for the duration of the protocol.

9. The subject uses tobacco products or any other products during nightly awakenings that may interfere with the sleep wake cycle.
10. The subject has any unstable medication condition as determined by the investigator, or any other serious disease or condition that might affect life expectancy or make it difficult to successfully manage and follow the subject according to the protocol.