



## • Research Article

# Hand self-Shiatsu for sleep problems in persons with chronic pain: a pilot study

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**OBJECTIVE:** Difficulty falling asleep (sleep latency) and staying asleep (sleep maintenance) are common problems for persons living with pain. Research demonstrates that sleep problems are, in turn, related to exacerbation of chronic pain. There is a growing body of evidence for a range of pragmatic, non-pharmacological sleep interventions that can potentially be incorporated into pain management programs. This study looks at the outcome of teaching patients with musculoskeletal pain standardized pre-bedtime hand self-Shiatsu (HSS) to reduce sleep latency.

**METHODS:** A case series design, with participants acting as their own controls, was selected to facilitate hypothesis generation for this novel, under-researched intervention. Sleep efficiency, latency and maintenance, sleep beliefs, pain intensity and basic participant demographics were collected at baseline with actigraphy and standardized self-report questionnaires. After one week of baseline data collection, the HSS intervention was taught to participants. Follow-up data were collected at 2 and 8 weeks post-intervention.

**RESULTS:** Data collected at baseline and the two follow-up periods revealed no apparent changes in the objective actigraphy data. However a trend toward improved self-reported sleep latency (time to fall asleep) and sleep duration (time spent asleep) emerged. A number of participants reported they were more concerned with increasing their period of unbroken sleep as opposed to their total sleep time and it is possible that HSS may be useful to be applied during nighttime awakenings as well as before bed. None of the participants reported adverse effects of the intervention.

**CONCLUSION:** These preliminary findings are promising and future studies exploring the mechanism of action and with stronger control of treatment fidelity are indicated.

**KEYWORDS:** Shiatsu; self-management; pain; sleep; insomnia; pilot study

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## 1 Introduction

There exists a strong relationship between disordered

sleep and chronic pain, which holds true from young children to older adults living in residential care facilities<sup>[1-5]</sup>. Traditionally, healthcare providers have conceptualized sleep problems (for example insomnia) as a consequence of chronic

pain and assumed that, as pain becomes better managed, restorative sleep patterns will return. However, current research points towards a bi-directional pain and sleep relationship where not only is sleep deficiency an outcome of pain, but sleep deficiency also appears to be a risk factor for developing and sustaining chronic pain<sup>[6]</sup>. This new perspective is of clinical interest because it highlights the potential importance of addressing sleep problems early in the course of pain intervention therapy.

There is a growing body of evidence for a range of pragmatic, non-pharmacological sleep interventions (NPSIs) that can be incorporated into pain management programs. Additionally, many NPSI strategies are controlled by the patient and, as such, are congruent with the patient self-management model favored by most pain services<sup>[7]</sup>. Many patients with chronic health conditions come to feel that they are powerless to affect change and that the future is largely unknown, with little to be hopeful about<sup>[8]</sup>. The patient self-management approach, based on psycho-educational principles, targets teaching active coping strategies and facilitates self-efficacy. Self-management approaches have been demonstrated in the literature to help patients regain feelings of mastery and control<sup>[9]</sup>. Introducing pragmatic NPSIs in pain self-management programs may provide additional opportunities to enhance patients' feelings of control and hopefulness.

One promising, but under-researched area is complementary and alternative medicine (CAM) sleep interventions for persons with chronic pain. Hand self-Shiatsu (HSS) is an example of such an intervention. HSS adheres to evidence-based principles pertaining to self-management<sup>[7]</sup>, because with appropriate training, patients can self-administer HSS. HSS is a practical tool because patients can administer HSS within the bio-psycho-social and environmental context of their own lives. It requires no special equipment and is unavoidably portable. Unlike many other body sites where massage and Shiatsu are performed the hand is usually accessible even when mobility is limited and can be accessed discretely such that privacy is not a particular issue. HSS can be done by someone with pain at any time and with little distraction to other people<sup>[10]</sup>. Once someone learns to perform HSS, there is likely to be no further cost. All of these factors make HSS a practical and accessible self-management strategy for sleep.

Shiatsu is based on the principles of traditional Chinese medicine. It uses pressure points found along the meridians, and has similarities to acupressure. Shiatsu practitioners apply thumb and finger pressure to specific points based on the theory that there is heightened neurological activity expressed in the muscles at these points<sup>[10]</sup>. As yet, there is no clear demonstration that the principles of traditional Chinese medicine are in play during HSS and additional mechanisms for the effects of HSS to reduce sleep problems

should also be considered. For example, since HSS is quite specific, a sustained degree of on-task concentration is required. Congruent with what we know about brain functioning, this level of concentration can hinder the individual from attending to other, competing and co-occurring thoughts<sup>[11]</sup>. Thus, actively carrying out HSS may preclude concentrating on negative thoughts and emotions. Other cognitive interventions to decrease rumination in persons with insomnia have been shown to be effective<sup>[12]</sup>; it is possible that the active concentration required to carry out HSS aligning with this approach. Furthermore, because HSS involves concentrating on a motor activity, as opposed to thoughts and feelings, it should be an acceptable therapy even to individuals who do not tolerate or respond to the interpersonal reflection components of other cognitive therapies.

This study is highly relevant because, as the authors of an International Association for the Study of Pain (IASP) global study of pain prevalence report, "chronic pain is among the most disabling and costly afflictions in North America, Europe, and Australia"<sup>[13]</sup>. They concluded from their review of published studies that the prevalence rate of severe chronic pain in adults is approximately 11% and ranged between 9.1%–55.5%<sup>[13]</sup>. Chronic pain is a complex interaction of bio-psycho-social factors and, as such, is often resistant to intervention<sup>[14]</sup>. Pragmatic, evidence-based self-management interventions are much needed. While there is a small body of evidence suggesting that body work in the form of massage is an effective sleep intervention for older adults in residential care<sup>[15]</sup> and for children with chronic health conditions<sup>[16,17]</sup>, to date self-administered body work (massage or Shiatsu) of any approach has not been tested with a working age, cognitively intact, adult population with chronic pain. This study begins to address this evidence gap.

As reported by Bennett and Closs<sup>[18]</sup>, NPSIs are best understood as complex interventions with highly interactive components and a combination of known and unknown components. Bennett and Closs call the outcomes of these interventions "bundled effects" where it is not possible to tease apart the contributing features of the different biological, contextual and psychological influences with the same linearity applied in pharmaceutical trials. They recommended study designs for non-pharmacological interventions where patients act as their own controls and that measure secondary outcomes, such as adherence and anxiety, in addition to the primary objective. Finally, they highlighted the importance of feasibility and pilot studies in complex interventions that lack strong theory about the mechanism of change. Congruent with these recommendations, the primary objective of this pilot study was to test whether a standardized HSS intervention demonstrates the capacity to reduce subjective and objective sleep latency. Secondary outcomes included: to determine if HSS was



acceptable to participants; if there were common patterns of sleep beliefs that would highlight areas for targeted patient education activities in the future; and if perceived pain intensity altered during the study period. This theory-building pilot study also allowed us to test the protocol and assessment tools in preparation for a large-scale project.

## 2 Materials and methods

Approval for this study was received from the Health Ethics Review Board, University of Alberta, Canada and all participants gave written consent to participate. The study used a case series design with participants acting as their own controls. Case series studies are well suited for hypothesis generation for novel interventions where a stronger evidence base does not yet exist<sup>[19]</sup>. Sleep latency and maintenance (actigraphy monitoring and self-report), sleep beliefs, pain intensity and basic participant demographics were collected at baseline. After 1 week of baseline data collection, the HSS intervention was taught to participants in one-to-one sessions by trained research assistants (with a background in either occupational or physical therapy). At 2 weeks and 8 weeks post-intervention, objective and subjective sleep measures and the other sleep and/or pain measures were collected again. The specific measurement tools are detailed below.

### 2.1 Participants

Participants were recruited through University of Alberta, Faculty of Rehabilitation Medicine affiliated clinics. Specific inclusion criteria were 18 years of age or older, able to communicate in English, no hand injuries or skin problems precluding HSS, a diagnosed musculoskeletal condition and self-reported problems with sleep. Inclusion criteria were deliberately broad so as to recruit as diverse a population of persons with musculoskeletal disorders as possible for this preliminary pilot work.

### 2.2 HSS rationale

The sleep-related evidence base for body work in the form of Shiatsu is extremely limited, therefore we also scoped the sleep intervention literature of other forms of body work. A recent systematic review of massage for low back pain<sup>[20]</sup> concluded that “massage might be beneficial for patients with sub-acute and chronic nonspecific low back pain, especially when combined with exercises and education”. The evidence suggested that acupressure massage was more effective than classic massage, but this needs confirmation<sup>[20]</sup>. Building on this sparse evidence, HSS was selected for this study because, based on traditional Chinese medicine principles, pressure points and meridians, HSS is similar to acupuncture and acupressure. While some reviews of massage for sleep and for pain exist<sup>[21]</sup>, and demonstrate promising findings, these studies all employed massage applied to the subject by someone else.

The person with pain is a passive recipient as opposed to actively being in control, which is generally considered a more desirable state. While there is some promising evidence for the effect of hand massage, the studies were carried out with frail elderly populations whose caregivers provided the massage<sup>[15,22]</sup>. No studies of self-Shiatsu for sleep problems were found. Because of this lack of foundational research, we developed our own protocol for pre-bedtime hand self-Shiatsu based on the clinical knowledge and skills of our co-investigator (LB), a certified Shiatsu therapist with over 10 years of clinical and workshop trainer experience at the time of this study. The protocol is available on request to the corresponding author.

### 2.3 Sleep actigraphy

The ActiSleep monitor (manufactured by ActiGraph, <http://www.actigraphcorp.com/>) and the accompanying analysis software were used in this study. The ActiSleep monitor records 24-hour activity in 60-second epochs and measures light exposure in lux between 350-850 nm. Actigraphy is widely used to objectively measure daytime activity, light exposure and night time sleep latency and maintenance<sup>[23]</sup>.

### 2.4 Secondary outcomes

These were recorded with a sleep log self-report modified to record frequency and outcome of nightly self-Shiatsu at both follow-up periods, a pain intensity visual analogue scale (VAS) and the Pittsburgh Sleep Quality Index (PSQI)<sup>[24]</sup>. The PSQI is a widely used, psychometrically strong, self-report measure of perceived sleep latency, recalled awakenings, and other variables that comprise an overall sleep quality score. Cronbach's  $\alpha$  is reported as 0.80 across groups with moderate to high correlations between global and component scores. The Sleep Beliefs Scale (SBS)<sup>[25]</sup> was used to investigate potential controlling variables. Psychometric testing of the SBS revealed good internal consistency (Cronbach's  $\alpha = 0.714$ ). We planned to include a beliefs scale because knowledge about sleep in the Canadian population overall is poor and we were interested to see if patterns of relationships emerge between beliefs, adherence to the HSS intervention and sleep latency, maintenance, and overall sleep quality as measured by the PSQI and actigraphy.

### 2.5 Participant-expected outcomes

We also added an open-ended question to better understand the potential clinical significance of the intervention and at the 8th week of follow-up we asked how many more minutes of sleep would participants need to achieve to feel that the time invested in doing the self-Shiatsu on a regular basis was worthwhile.

### 2.6 Data analysis

Descriptive statistics were used to summarize the primary and secondary outcomes. Ratio level data were presented as means and standard deviations. Non-ratio level data were summarized as frequencies and percentages. We

used SPSS to summarize the data (SPSS Inc. Released 2009. PASW Statistics for Windows, Version 18.0. Chicago: SPSS Inc.). Qualitative data were summarized verbatim.

### 3 Results

#### 3.1 Participants

Of the original 14 volunteers, 3 men and 9 women completed the study ( $n=12$ ). The mean age was 58.4 years, with a range between 45 and 71 years. The average duration of pain was 14.8 years, with a range between 2 to 30 years (standard deviation 9.48 years). Five participants reported that they slept alone in bed, 1 slept alone in a recliner, 4 shared the bed with a partner, and 2 shared the bed with pets. Participants identified having between 1 to 5 pain sites. The identified sites were diverse and included hip, knee, shoulder, neck, low back, sciatic, wrist, jaw, sternum, intercostal, plantar fasciitis and migraine pain. The most frequently identified pain site was back ( $n=7$ ), followed by shoulder, hip, and knee, which were each identified by four participants. Five participants (41.7%) reported sleep problems existed prior to onset of any pain and 7 (58.3%) said they were sleeping well prior to pain onset.

All participants reported having tried 3 or more forms of sleep interventions in the past. Prescription medica-

tion was most common (58.3%,  $n=7$ ), followed by music, exercise/activity, hot or cold packs, and herbal remedies (25%,  $n=3$ ), over the counter medication, relaxation, distraction, meditation, warm baths, positioning pillows, and yoga (16%,  $n=2$ ), and finally, melatonin, physiotherapy, orthotics, humidifier, and general sleep hygiene were each mentioned once (8.3%,  $n=1$ ). Nine of the participants (75%) reported past experience with complementary and alternative health care.

Participants for the most part were non-smokers and drank alcohol infrequently or not at all. Their reported caffeine consumption ranged from 0 to 250 mg/d at the start of the study and from 0 to 465 mg/d at the end of the study. These figures were approximated based on the detail provided about the number of ounces consumed and detailed description of the beverage.

#### 3.2 Sleep beliefs

Participants endorsed each of the sleep statements in the SBS<sup>[25]</sup> as having either a positive, neutral or negative effect on sleep. Most participants were aware that the pre-bedtime activities of drinking caffeinated beverages, doing intensive work and study, having a heavy meal, and worrying about going to sleep would have a negative effect on sleep (Table 1). However, they were less consistently aware of the negative impact on sleep of most other activities, and

**Table 1** Sleep beliefs scale

Belief statement	Positive effect ( <i>n</i> (%))	Neutral effect ( <i>n</i> (%))	Negative effect ( <i>n</i> (%))	Total participants with incorrect response ( <i>n</i> (%))
Drinking alcohol in the evening	0 (0.0)	4 (33.3)*	8 (66.7)	4 (33.3)
Drinking caffeine beverage after dinner	0 (0.0)	1 (8.3)	11 (91.7)	—
Intense physical exercise before bed	1 (8.3)*	2 (16.7)*	9 (75.0)	3 (25.0)
Long nap in daytime	0 (0.0)	4 (33.3)*	8 (66.7)	4 (33.3)
Same bedtime and getting up time	8 (66.7)	2 (16.7)*	2 (16.7)*	4 (33.3)
Thinking about next day's activities before sleep	1 (8.3)*	2 (16.7)*	9 (75.0)	3 (25.0)
Regular sleep medication	3 (25.0)	4 (33.3)	5 (41.7)	—
Smoking before falling asleep	2 (16.7)*	4 (33.3)*	5 (41.7)	6 (54.5)
Relaxing before bed	8 (66.7)	2 (16.7)*	2 (16.7)*	4 (33.3)
Going to bed 2 hours later than usual	2 (16.7)*	5 (41.7)*	5 (41.7)	7 (58.3)
Going to bed with empty stomach	3 (25.0)	2 (16.7)	7 (58.3)	—
Using bed for non-sleep activities (e.g., TV and phone calls)	1 (8.3)*	3 (25.0)*	8 (66.7)	4 (33.3)
Trying to sleep when not tired	1 (8.3)*	3 (25.0)*	8 (66.7)	4 (33.3)
Studying/working intensely until late night	0 (0.0)	2 (16.7)*	10 (83.3)	—
Getting up when can't fall asleep	7 (58.3)	2 (16.7)*	3 (25.0)*	5 (41.7)**
Going to bed 2 hours earlier than usual	1 (8.3)	1 (8.3)	10 (83.3)	—
Going to bed right after a meal	0 (0.0)	1 (8.3)	11 (91.7)	—
Ruminating about not getting enough sleep	0 (0.0)	0 (0.0)	12 (100.0)	—
Sleeping in a quiet and dark room	11 (91.7)	1 (8.3)	0 (0.0)	—
Making up lost sleep by sleeping for a long period	2 (16.7)*	3 (25.0)*	7 (58.3)	5 (41.7)

\*: inaccurate belief; \*\*: although congruent with traditional sleep hygiene recommendations the usefulness of this strategy is now being called into question.

particularly about the negative effect of smoking before bed, going to bed later than usual schedule and of sleeping in to make up for lost sleep (Table 1).

### 3.3 Sleep quality indicators

Because of dropouts, complete data from all three periods are available for only nine participants. Although the sample was insufficient to draw statistical conclusions, a trend emerged in the PSQI scores toward improvements in sleep latency and sleep duration across the three measurement periods (baseline, 2-week and 8-week follow-ups). The other PSQI components (subjective quality of sleep, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daily dysfunction) and the global score appeared to show no difference over time.

These self-reported differences were not evident in the actigraphy reports and no apparent difference across the three time periods was noted for sleep latency, total time asleep, frequency of nighttime awakenings and sleep efficiency. However, the mean sum of minutes awake during the sleep period was quite varied across all three times (79.56 min at baseline, 64.08 min at the 2-week follow-up and 75.55 min at the 8-week follow-up) and this may demonstrate a positive trend towards less frequent awakenings during the sleep period while treatment fidelity was highest.

### 3.4 Adherence to self-Shiatsu protocol

As detailed in Table 2, adherence to the protocol was better at the start of the study and fell off at the 8-week

follow-up. Reasons participants gave for not completing the self-Shiatsu protocol included that they fell asleep while engaged in the process. Other comments, hand-written into the form, indicated that a number of participants felt the process took too long or that they forgot to do it until it was “too late to bother because I knew I was falling asleep”.

### 3.5 Participant-expected outcomes

Seven participants answered this question and their responses ranged between additional 15 to 45 min with a mean of 32.85 min. The written comments reflected a concern not so much with additional sleep, but rather with less broken sleep. For example “*It is not the minutes of sleep overall – it is the length of the period of uninterrupted sleep. I would like 30 minutes more uninterrupted sleep*” (Participant J14).

### 3.6 Pain self-report

There was little apparent change in pain reported on the VAS on wakening, at noon or before bed across the three time periods of the study.

## 4 Discussion

This pilot study of HSS included participants who had a diverse range of pain sites and duration, as well as previous experience with CAM interventions. The primary objective of this pilot study was to test whether a standardized HSS

**Table 2** Protocol adherence

Adherence variable	Two-week follow-up (n (%))	Eight-week follow-up (n (%))
Self-Shiatsu before bed for nights monitored by actigraphy		
● 100% of nights	8 (66.7)	4 (33.3)
● 60%-99% of nights	3 (25.0)	3 (25.0)
● 30%-59% of nights	0	0
● <30% of nights	0	2 (16.7)
● Missing data	1 (8.3)	3 (25.0)
Total	12	12
Self-Shiatsu completed for nights monitored by actigraphy		
● 100% of nights	4 (33.3)	0
● 60%-99% of nights	4 (33.3)	5 (41.7)
● 30%-59% of nights	2 (16.7)	0
● <30% of nights	1 (8.3)	3 (25.0)
● Missing data	1 (8.3)	4 (33.3)
Total	12	12
If self-Shiatsu not completed — why?		
● Fell asleep during the therapy	4 (33.3)	1 (8.3)
● Too tired	1 (8.3)	1 (8.3)
● Forgot	2 (16.7)	4 (33.3)
● No reason offered	5 (41.7)	5 (41.7)

intervention had the potential to result in a trend toward improved subjective and objective sleep efficiency. While there were no apparent changes in the actigraphy data we did find a trend toward improved self-reported sleep latency (time to fall asleep) and sleep duration (time spent asleep). Although the sample was of insufficient size to draw strong conclusions, we cautiously interpret these findings as promising. The importance of subjective perception of restful sleep in addition to objectively measured sleep parameters is well documented in the literature<sup>[26]</sup> and it is possible that with stronger adherence to the HSS protocol we may achieve objective improvements in sleep parameters as well.

One secondary outcome of interest was to determine if HSS was acceptable to participants. While a number stated that it took a long time to complete the HSS, none of the participants said the procedure was unacceptable, painful or distressing in any way. This is encouraging and supports the potential that this non-obtrusive, portable, low-cost, NPSI holds, and warrants further study. Identifying areas for more targeted sleep knowledge education for persons with pain was an additional objective. The HSS was not intended to change sleep beliefs and, as expected, participants' attitudes and beliefs about sleep remained consistent across the timespan of the study. From these findings we were able to determine several areas where a third or more of the participants had inaccurate or insufficient information. Of particular note was the lack of knowledge about the negative effect of smoking before bed, going to bed later than one's usual schedule, and of sleeping in to make up for lost sleep. Knowledge translation (KT) research identifies that contextualized and targeted information is more likely to be acted upon<sup>[27]</sup> and this lesson from the KT field can help us strategize how to address counter-productive sleep beliefs and attitudes that can increase the likelihood of sleep deficiency in persons with chronic pain.

The final objective of the study was to contribute to theory building and test the protocol and assessment tools in preparation for a larger-scale project. There were several key lessons from the pilot we can address for future work. Firstly, we will attempt to decrease the amount of time the HSS procedure takes to complete from its current 12-15 min to between 7-10 min. We know that most people fell asleep while carrying out the procedure so we will next test if HSS is also a useful strategy to assist in return to sleep during nighttime awakenings.

Our pilot did not allow us to determine what mechanisms were at play in HSS and the self-reported decrease in sleep latency. Although at this point we can only speculate there are several possibilities building on the existing evidence. Firstly, improved sense of wellbeing and self-efficacy are hallmark goals of cognitive interventions for persons with pain. A review of unanticipated benefits of CAM

therapies for back pain revealed that CAM interventions can result in increased hope, relaxation, positive mood, body awareness, and feelings of well-being and ability to cope<sup>[28]</sup>. It may be that the HSS intervention contributed to these feelings in participants, which in turn helped improve pain management such that sleep latency was decreased. A second possibility is that the HSS affected the balance of energy through Shiatsu's application of pressure to specific points along the body's meridians<sup>[29]</sup>. Robinson *et al's* review<sup>[29]</sup> of Shiatsu found clear evidence for pain reduction and improved sleep in the institutionalized elderly persons. However, none of the reviewed studies used self-Shiatsu. Rather, these studies were based on participants being the passive recipients of applied Shiatsu and it is possible that the application of self-Shiatsu mediates sleep and pain responses differently. For example, self-Shiatsu seems more congruent with the self-management goal of pain intervention and therefore may align with cognitive-emotional mechanisms as well.

A third mechanism we did not consider in the study design was the influence of gender on perception of sleep quality. There is little background research in this area but a recent study suggested that, while men's ratings of sleep quality reflected the duration of sleep, women's ratings were more influenced by the number of awakenings over the course of the sleep period<sup>[30]</sup>. There were more women than men in our study and this may have been an unanticipated bias. It would be important to recruit larger samples so that this potential influence can be fully examined.

Finally, we speculated that the HSS serves as a transition activity that assists sleep onset because of the cognitive demand it places on the participant. Unlike the rumination and cyclical thinking that are reported as common pre-sleep activities<sup>[6]</sup>, the cognitive task of HSS is not anxiety inducing nor alerting in the same manner as stressful cognitions that can activate sleep-delaying physiological responses. We considered it might be possible that the psychological mechanism activated through HSS is that of attention processing where competing demands on the attentional system are incompatible, and cannot be sustained simultaneously. In the case of HSS, the cognitive demand of remembering the HSS sequence would compete with the demand of typical sleep-negative pain-related bedtime rumination. Competing attentional demand is an area receiving increasing focus in the research literature; whether attentional capacity is a single finite resource that needs to be shared between competing demands or if attention can be achieved through multiple resources is still a topic of controversy<sup>[11]</sup>. The development of attentional processing research offers rich opportunities for further investigation of the active mechanism(s) of HSS.

There are limitations readers should be aware of when interpreting our findings. Specifically, this pilot study



was not powered to enable a reliable testing of our findings statistically or consider covariates such as gender. In addition, we had not established a mechanism to facilitate intervention fidelity so it is possible that participants over- or under-reported their use of HSS. However, in spite of these limitations, we believe the HSS pilot demonstrated promising findings for a relatively heterogeneous population of persons with pain and served to refine the research questions that need to be addressed for further theory building and testing. We are preparing a large study with a more contextually homogeneous population where we will further explore the attentional capacity aspects, decrease the time it takes to complete the HSS, include HSS use for nighttime awakenings in addition to the current pre-bed application and implement strategies to better control for treatment fidelity and potential gender bias.

### 5 Conclusions

Considering the bi-directional relationship between pain and sleep, effective sleep interventions are much needed by the substantial population of people in chronic pain. HSS is a tool that facilitates self-efficacy through self-management of pain-related sleep inefficiency, and may hold potential as an effective sleep intervention. The results from this study suggest that HSS is feasible, acceptable and demonstrated subjective and objective trends for enhanced sleep efficiency. Future research is warranted to more definitively evaluate the effectiveness of HSS as well as clarify its mechanism(s) of action.

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### 7 Competing interests

The authors declare that they have no competing interests.

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## Submission Guide

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