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Living Legends in Sleep Research

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How openness and inquisitiveness led to a career as a sleep researcher and a broad contribution to sleep science

Timothy Roehrs*

Sleep Disorders & Reseach Center, Henry Ford Health, and Department of Psychiatry and Neuroscience, Wayne State University, School of Medicine, Detroit, MI, USA
*Corresponding author. Timothy Roehrs, Sleep Disorders & Research Center, Henry Ford Hospital, 2799 West Grand Blvd, CPF-3, Detroit, 48202 MI, USA. Email: troehrs1@hfhs.org

Abstract

After describing my serendipitous discovery of sleep research as a potential career, I note how my openness and inquisitiveness led to a broad contribution to sleep science. After a PhD in biological psychology, I completed a postdoctoral fellowship in alcoholism and drug abuse. This led to my first studies on rebound insomnia. I then describe early studies on the relation of sleep continuity/sleep time to daytime sleepiness and function. This led to studies of how basal sleep time/sleepiness interacts with the effects of sedating and alerting drugs. Several collaborations led to studies on sleep and hot flashes in perimenopausal women and on sleep and acute and chronic pain.

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Key words: sleepiness; sedating drug effects; alcohol effects; hypnotic abuse risks

Introduction to Sleep

My introduction to sleep was serendipitous. As a new MA clinical psychology student at Xavier University, Cincinnati Ohio I received a newly created research assistantship (RA) at the VA Hospital Sleep Center, Cincinnati, Ohio under the direction of Thomas Roth PhD and Milton Kramer, MD. I knew nothing about sleep but was open to learning. Dr Roth, my RA mentor, guided me in readings on the basics of sleep and taught me to score sleep using the Rechtschaffen and Kales scoring rules. My first task was to score sleep recordings collected in a large "sonic boom" study funded by the Federal Aviation Administration in which "booms" were periodically delivered through large speakers positioned next to the beds of sleeping healthy volunteers. At that time there was concern regarding the impact of super-sonic jet travel across the US. Vaguely, I remember the results as the "booms" only disrupted the sleep of the middle-aged volunteers; younger volunteers slept through the "booms" and the older volunteers were awake so much of the night that the "booms" did not further disturb their sleep.

The APSS, Association for the Psychophysiological Study of Sleep (the predecessor to the Sleep Research Society), held international meetings, and Dr Roth invited me to attend the APSS meeting held in Bruges Belgium in June 1971. The Queen of Belgium opened the meeting and many of the sleep scientists I had read about were in attendance. Dr. Roth made sure to introduce me to Dr. Alan Rechtschaffen and Dr. Bill Dement. I was hooked.

To confirm my career switch after my MA, from clinical psychologist to sleep researcher, I took a RA position at the Pharmacology Department, University of Cincinnati SOM under the direction of Dr. Naim Khazan. Dr. Khazan was continuously recording sleep in drug-naïve or physically dependent rats receiving investigator-administered or self-administered morphine and methadone [1]. Both drugs were initially highly REM-suppressive, the rats showed tolerance development, and when the drug was discontinued expressed, a sustained REM rebound. These findings were significant in that at this point no studies of morphine or methadone effects on sleep in *drug-naïve* organisms had ever been done. The French equivalent of NRP came and filmed me and our self-administering rats. It was gratifying to be on the leading edge of sleep and drug abuse science and my career choice was confirmed.

To summarize, I was open to a career switch and a new research field I knew nothing about. Those early experiences of mine form the theme of this article, the importance of openness/inquisitiveness in a sleep research career.

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Openness/Inquisitiveness in Understanding Research Findings

The first sleep research study of mine, my master's thesis, illustrates the importance of openness/inquisitiveness or *the lack thereof* [2]. The thesis investigated how sleep physiology affects mood change from night to morning. Standard 8 hours Rechtschaffen & Kales polysomnographic (PSG) sleep recordings were collected in 11 healthy volunteers who slept on 14 consecutive nights. The Clyde Mood Scale, a 48-adjective checklist with ratings labeled not at all, a little, quite a lot, and extremely, was administered before sleep and in the morning upon arising. Over the 14 nights five randomizations of the listing of the 48 adjectives were utilized. The checklist was factor-analyzed into six subscales friendly, aggressive, clear-thinking, sleepy, unhappy, and dizzy. I hypothesized improvements in a positive direction on the mood subscales would be related to the various sleep parameters with my focus on friendliness and happiness.

Among the strongest correlations ($r = .42$) were sleep latency and stage 3–4 sleep which correlated with night-to-morning improvements in the sleepy and friendly subscales. The friendliness outcome supported my hypothesis, but sleepiness? I dismissed the significance of the sleepy subscale correlations as it seemed obvious that the better one slept at night the less sleepy one would feel in the morning. I dismissed this finding. Little did I appreciate that this symptom, sleepiness, would be significant in the development of the field of clinical sleep medicine.

I went on to earn a PhD in Biological Psychology at the University of Georgia and did a postdoctoral fellowship at the Institute of Alcoholism and Drug Abuse at the University of Washington, Seattle. There I learned the principles of psychopharmacology and the background literature and methods for the study of alcoholism and drug abuse. This background formed the basis for my career in sleep and sleep medicine. After my postdoctoral fellowship I re-joined Dr. Tom Roth who was then the Director of the newly established Sleep Disorders & Research Center (SD&RC) at Henry Ford Hospital in Detroit MI. The SD&RC was among the twelve founding members of the American Association of Sleep Disorders Centers, the predecessor body to the American Academy of Sleep Medicine.

In addition to a full clinical practice at the SD&RC, attended by two sleep disorders physicians, the center conducted many single-site hypnotic clinical trials in which I was able to participate as a co-investigator. Two Sandoz Pharmaceutical Company funded temazepam hypnotic efficacy trials supported my salary until I was awarded my first NIH grant in 1986. The grant assessed the dose determinants of rebound insomnia in healthy volunteers using the short-acting benzodiazepine hypnotic triazolam [3]. After six nights of placebo, triazolam 0.25 mg, or 0.50 mg (a supra-clinical dose), placebo was substituted on night seven. Increased wake time relative to baseline (the accepted definition of rebound insomnia) was found with the 0.50 mg dose, but not the 0.25 mg dose or placebo. Further, on night six, before the night seven rebound test, relative to placebo, both active doses increased total sleep time (TST), although the 0.50 mg dose provided no greater hypnotic efficacy than the 0.25 mg dose. The study results indicated that rebound insomnia has a clear pharmacological basis and is only associated with supra-clinical doses.

Early career studies of risks associated with hypnotic use

Unlike my first response to my research results, I continued to pursue questions around rebound insomnia. One of the most important clinical questions regarding rebound insomnia is the extent to which it leads to drug abuse/dependence. A study combined human self-administration techniques, as learned on my post-doctrinal fellowship, to assess dependence liability with the dose-related effects of rebound insomnia [4]. The persons with insomnia and healthy volunteers were randomized to three discontinuation methods after six nights of 0.5 mg triazolam or placebo: (1) abrupt discontinuation of 0.5 mg triazolam with placebo substitution, (2) a tapered discontinuation (three nights of 0.50 mg, two nights of 0.25 mg, and one night of 0.125 mg), and (3) a placebo discontinuation for the placebo group. Following the discontinuation participants were given an opportunity to self-administer their assigned treatment medication. Overall, I found low self-administration rates, and those rates did not differ among the three discontinuation methods, suggesting rebound insomnia did not enhance the likelihood of continued hypnotic self-administration.

I then studied whether acute duration of administration of a supra-clinical hypnotic dose would alter the likelihood of rebound insomnia [5]. After 1-, 6-, and 12-nights administration of triazolam 0.5 mg or 12 nights of placebo in healthy volunteers, there was no difference as to treatment duration. Relative to placebo sleep efficiency was reduced on the treatment discontinuation night (rebound insomnia) similarly after the three different treatment durations. However, there were individual differences in the expression of rebound insomnia; those healthy volunteers with poorer baseline sleep were more likely to express rebound.

Since it was well established that rebound insomnia was associated with supra-clinical doses, I investigated whether there were circumstances under which a *clinical* dose would lead to rebound. Zolpidem was approved as a hypnotic in 1992 and it quickly became the most frequently prescribed hypnotic in the US. While it has a different chemical structure than the benzodiazepine hypnotics, it acts at the benzodiazepine receptor complex. A zolpidem study assessed whether long-term hypnotic use at clinical doses would enhance the likelihood of rebound insomnia [6]. Persons with insomnia were randomized to 12 months of nightly zolpidem 10 mg or placebo. At month 1, 7, and 12 placebo was substituted for active drug for seven nights. Sleep efficiency (TST/TIB) was not worsened relative to baseline during the rebound test nights in months 1, 7, and 12 (i.e., no rebound insomnia). Relative to placebo sleep efficiency remained increased through month 12 (i.e., long term efficacy), which is one of the first PSG studies to show long-term efficacy of a hypnotic. Overall, these studies showed the conditions for, and the risks associated with rebound insomnia. This remains valuable information for physicians prescribing hypnotics.

Early career studies of sleep time and sleepiness

As a standard protocol at the SD&RC, irrespective of their presumptive diagnosis, all patients received a multiple sleep latency test (MSLT) during the day following their nocturnal polysomnogram (NPSG), reflecting the brilliance of Dr. Tom Roth as a clinical sleep researcher. One group of patients stood out in that they expressed pathological sleepiness (MSLT average sleep latency ≤5 minutes) with no evidence of a nocturnal sleep disorder. I was the first to report among sleep disorders patients with evidence for chronic insufficient sleep due to reduced time-in-bed (TIB) as a cause of pathological daytime sleepiness assessed objectively by the MSLT [7]. I then observed the same level of MSLT-defined pathological sleepiness in 20% of a large sample of research volunteers, all denying daytime sleepiness [8]. In several follow-up

studies I showed that a 10-hour enforced TIB in such volunteers restored normal levels of sleepiness/alertness in a one-week and a two-week study [9]. I also joined my colleague, Dr. Tom Roth, as Co-Investigator in a NIH-funded grant assessing level of MSLT-defined sleepiness and its correlates in a representative sample of the general population of SE Michigan [10]. Among the significant correlates to the excessive daytime sleepiness (MSLT < 6 minutes) found in SE Michigan was an increased automobile accident rate verified with the State of Michigan Office of Motor Vehicles.

I then continued by investigating how sleepiness interacts with drug and alcohol effects. Given the reported high-rates of stimulant use among young adults, in two consecutive NIDA grants I showed that the basal level of MSLT-defined sleepiness modified the performance and reinforcing effects of methylphenidate [11, 12]. In these studies, basal state of sleepiness was manipulated by reducing TIB the previous night. First, in healthy young volunteers I showed a 10 mg bid methylphenidate dose versus placebo increased MSLT mean sleep latency after both 8 hours and 0 hour TIB the previous night. Divided attention and vigilance performance scores were improved only after the 0 hour TIB condition. In another study healthy young volunteers in a forced choice protocol self-administered methylphenidate 10 mg versus placebo during the day after 4 hours TIB the previous night, but not after 8 hours TIB. Finally, to assess the dose-related effects of the interaction of sleepiness and stimulant self-administration, healthy volunteers were randomized to methylphenidate 5 mg, 10 mg, and 20 mg and self-administered their assigned dose after 8 h or 4 hours TIB [13]. Again, methylphenidate was self-administered vs placebo after 4 hours, but not 8 hours and there were no dose effects in self-administration rates. After 4 hours TIB choice rates versus placebo were 60–80% (reflecting a methylphenidate preference vs. placebo) and after 8 hours 20–30% (no preference). In these studies, validated drug effects questionnaires assessed the subjective effects of methylphenidate and regardless of TIB the previous night methylphenidate was experienced as a stimulant. In these short-term studies the results indicated methylphenidate was experienced as a stimulant, using validated drug effects questionnaires. In conclusion, healthy volunteers used methylphenidate to reverse sleepiness, and has a low short-term abuse liability. But the question remains regarding the risk of long-term use and the possibility of tolerance development and dose escalation.

Sleep time/sleepiness interaction with the effects of alcohol on daytime function.

Knowing the prevalence of sleepiness in sleep disorders populations and in the general population the question arose as to how this basal level of sleepiness may interact with the sedating and performance disruptive effects of alcohol. I used the alcohol administration methods I learned on my post-doctrinal fellowship to assess alcohol effects on MSLT-defined sleepiness, performance, and simulated automobile driving. In two consecutive NIAAA grants I showed that basal level of MSLT-defined sleepiness because of reduced TIB potentiated the effects of alcohol. Healthy volunteers were randomized to receive al 0.4, 0.6, or 0.8 g/kg doses of alcohol in the morning, and MSLT sleep latency was tested the rest of the day, which occurred after 8 hours and five nights of 5-hour TIB [14]. To provide context for the alcohol doses, 0.4 g/kg yields a breath ethanol concentration (BEC) = 0.03%, 0.6 g/kg = 0.05% and 0.8 g/kg = 0.07% and BEC >0.05% is legal intoxication in many states [15]. Mean next-day MSLT sleep latency differed as a function of dose after 8 hours TIB. After five nights of 5 hours TIB mean MSLT sleep latency did not differ by dose and was 5 minutes or less (i.e., excessive sleepiness) for all dose groups. This study design modeled a typical work week for the many in the general population with restricted bedtimes on workday nights.

Another study of the interaction of sleepiness with the effects of alcohol (0.6 g/kg) focused on divided attention (DAT) performance and simulated automobile driving [16]. Twelve healthy volunteers served in four conditions: 8 hours TIB + placebo, 4 hours TIB + placebo, 8 hours TIB + alcohol, and 4 hours TIB + alcohol, presented in a Latin Square design. Unlike our previous studies in which a single dose was administered at 9 am we provided supplemental doses (0.2 g/kg) at 10:30 and 11:00 am, which was done to maintain BEC at 0.50% throughout the am simulated driving testing. Multiple sleep latency test and performance testing was done at the HFH SD&RC site on day one, and on day two performance testing and simulated driving were done at the University of Michigan Transportation Institute. On day 1 at HFH SD&RC MSLT mean latency was reduced after 8 hours-placebo from 10.7 minutes to 6.3 minutes after 4 hours-placebo; 6.1 minutes after 8 hours-alcohol, and 4.7 minutes after 4 hours-alcohol. DAT reaction times after sleep restriction nights were slowed on the two days at both testing sites and after both TIBs in the alcohol conditions vs the placebo conditions. Most importantly, relative to placebo simulated driving deviations were increased in the two alcohol conditions with 4 hours-alcohol deviations greater than 8 hours-alcohol deviations. Further, on the afternoon alcohol driving tests with BEC approaching zero, quite *similar* driving impairment to that of the am testing was observed. This series of studies showed sleepiness interacts with alcohol, at BECs *below* legal intoxication in most states, to enhance the sedating, performance, and simulated driving disruptive effects of alcohol. These studies contributed to a National Institute of Alcoholism & Alcohol Abuse educational pamphlet released for the public. However, we also found the alcohol-sleepiness interaction is *bidirectional*. That is enhancing alertness (i.e., reducing sleepiness) reduces the sedative and impairing effects of alcohol [17]. Healthy volunteers received alcohol 0.75 g/kg (BEC = 0.06%) or placebo in the morning at 9:00 am after 8 hours TIB and then again after seven nights of 10 hours TIB. Alcohol shortened MSLT mean sleep latency from 17 minutes to 10 minutes in the 8 hours TIB and while the 10 hr TIB produced a slight increase in mean sleep latency, alcohol *did not* significantly reduce average MSLT sleep latency. Average MSLT sleep latency was like that of the placebo 8 hours TIB.

Further, it is known that there is a circadian rhythm to sleepiness/alertness as measured by the MSLT with midday latencies dipping and evening latencies increasing [18]. Twelve healthy volunteers received 0.05 g/kg alcohol or placebo at 09:00 am and 05:00 pm which was followed by MSLT testing, consisting of four tests at 2hr-intervals after each time of beverage administration [19]. Mean MSLT sleep latency after placebo was longer after the 05:00 pm consumption than the 09:00 am consumption (the known circadian variation of sleepiness/alertness). Mean sleep latency after alcohol was reduced after the 09:00 am consumption, *but not* the 05:00 pm consumption. DAT performance was tested 2 hours after each beverage administration. DAT z scores were reduced after the morning alcohol consumption, but not the 05:00 pm consumption. These two studies suggest the alcohol-sleepiness interaction is bidirectional.

Studies of the risks of using alcohol as a sleep aid in insomnia.

In an epidemiologic study of the Detroit metropolitan area 18% of respondents reported they used alcohol as a sleep aid [20]. This

information led to any number of questions around the use of alcohol as a sleep aid (i.e. does alcohol objectively improve sleep, throughout the night, at what doses, for whom and for how long and what are the risks associated with such use of alcohol) which I investigated in a series of NIAA-funded studies.

Healthy volunteers, with and without insomnia disorder, received on two separate nights 0.5 g/kg alcohol or placebo in color-coded cups before sleep [21]. On three subsequent nights participants chose their preferred pre-sleep beverage (0.2 g/kg or placebo) based on cup color and their experience on the sampling nights. They also were given an opportunity for three additional refills (0.2 g/kg) of their chosen beverage at 15 minutes intervals, yielding a total possible dose of 0.8 g/kg. The people with insomnia chose alcohol 67% of nights and the healthy volunteers 22%. The people with insomnia chose more alcohol refills than the healthy volunteers for an average nightly dose of 0.45 g/kg, while the healthy volunteers took more placebo refills. The PSGs collected on the two sampling nights, one alcohol and one placebo, reflect the effect of alcohol on the sleep of the two different participant groups. The 0.5 g/kg alcohol vs placebo reduced REM sleep for the whole night in both groups. Stage 3-4 sleep vs placebo was increased, and stage 1 sleep reduced in the people with insomnia to the levels of the healthy volunteers. Pre-sleep Profile of Mood tension and concentration subscales were improved on alcohol nights. We concluded in the short term the elevated alcohol choice rates in the people with insomnia were associated with positive sleep and pre-sleep mood effects.

The compelling question then was how these apparent positive effects of alcohol for the people with insomnia may change with repeated nightly use [22]. Twenty-four healthy people with insomnia disorder and no other medical, psychiatric, or drug abuse histories were randomized to one of three alcohol doses (0.0 g/kg, 0.3 g/kg, and 0.6 g/kg) administered before sleep for 6 consecutive nights. Eight-hour PSGs were collected each night. Total sleep time and stage 3–4 sleep were increased by night two with the 0.6 g/kg dose relative to placebo, but the improvement was lost by night 6. The benefits of alcohol to the people with insomnia were lost by night six, reflecting tolerance development. Incidentally, the data of this study and the previous study also address a dispute in the literature as to whether alcohol increases stage 3–4 sleep. It increased stage 3–4 sleep only in individuals with deficiency in stage 3–4, relative to age-matched normals.

In a follow up study, 12 volunteers with insomnia disorder were randomized to one of two treatment groups: 6 nights of 0.45 g/kg or placebo [22]. Then on each of two sampling nights they received placebo or alcohol 0.45 g/kg followed by seven choice nights. On choice nights they had the option, based on cup color, of choosing a cup with 0.2/kg alcohol and an additional three refills for a nightly possible total dose of 0.8 g/kg. The alcohol pretreated group choose alcohol on 54% of choice nights and the placebo pretreated group 37%. The alcohol pretreated group chose to double the number of refills to that of the placebo pretreated group. These data remain the only data to explicitly show the risks associated with the use of alcohol as a sleep aid in people with insomnia disorder.

Openness to Collaborations

Studies of sleep-in menopausal women

My openness to respond to invitations to collaborate on research in areas in which I had no knowledge base has led to significant contributions regarding the importance of sleep to the literature of that research area. As I reached mid-career, I had developed sufficient confidence in my sleep expertise such that I was comfortable in entertaining opportunities to collaborate as the "sleep expert."

In the early 2000s I received a call from Dr. Robert Freedman at the Department of Psychiatry & Neurosciences, WSU, who was an electrophysiologist studying "hot flashes" n perimenopausal women using sternal skin conductance to document the "hot flash." He attempted to add EEG recordings to document sleep and its stages. He invited me to review his recordings since in a preliminary paper he had reported that the "hot flash" disrupted slow wave sleep to cause an awakening and the women's report of a "hot flash." He had already validated that elevations in skin conductance were correlated with reports of "hot flashes." On review of the EEG tracings, it was clear to me that the rise in skin conductance was associated with sweat artifact which he was interpreting as slow EEG waves. After discussions we outlined a series of studies to assess the sleep related effects of "hot flashes," funded by NIMH over ten years.

In our first study healthy postmenopausal women, symptomatic and asymptomatic, and pre-menopausal women received 8 hours NPGS with simultaneous sternal skin conductance recording and MSLT the following day [23]. There were no differences in sleep time, arousals, and sleep staging among the three groups of women. The symptomatic women had about five hot flashes during the night and 46% of arousals from sleep occurred before and 46% after the hot flash and 6% simultaneously. There were no MSLT differences among the groups. We concluded there was no evidence that hot flashes uniquely disturbed sleep or produced daytime sleepiness.

Because hot flashes are an exaggerated heat dissipation response and it was known that during the day hot flashes occurred less frequently in cold relative to warm ambient temperatures, we studied hot flash occurrence during sleep in 30C (86F), 23C (73F), and 18C (64F) degree ambient bedroom temperatures [24]. Further, because it is known thermoregulation is absent during REM sleep, we compared hot flash frequency in the first 4 hours versus the last 4 hours (when REM sleep predominates) of the 8 hours sleep recording. We recruited symptomatic, asymptomatic, and cycling women. Unlike the previous study, the symptomatic women had more arousals and awakenings than the other two groups, but only in the first 4 hours of the night. This difference did not occur in the second 4 hours of the night. In the first half of the night most hot flashes preceded arousals and awakenings (regardless of sleep stage), while in the second half this pattern was reversed. Finally, as during the daytime, hot flashes were reduced in the 18 C degree ambient temperature bedroom. This study explained many of the literature discrepancies between hot flash self-reports, sleep disturbance and laboratory-reported data.

Finally, to determine whether the prevalence of poor sleep reports among menopausal women may reflect the known age-related increase in prevalence of primary sleep disorders (i.e., apnea and periodic limb movements) in post and perimenopausal women, we recruited 102 women, aged 44–56 years [25]. They were assessed with the Pittsburgh Sleep Quality Index (PSQI), the Hamilton Depression and Anxiety Indices and a complete clinical NPSG. Our assessment results were analyzed by multiple regression (SAS Institute, Cary NC; MAXR) analyses. Fifty-three percent of the women had apnea, periodic leg movements, or both. The best predictors of subjective sleep quality on the PSQI were the

Hamilton Anxiety Index scores and the number of hot flashes in the first half of the night. The best predictors of NPSG sleep efficiency were number of apneas, leg movements and arousals. We concluded the presence of primary sleep disorders is a significant factor in contributing to a menopausal women's sleep complaints beyond the experience of hot flashes. These studies were the first objective documentation of the relation of hot flashes and sleep. They resolved questions in the literature and clarified some of the myths around hot flashes and sleep.

Studies of chronic and acute pain

My studies of sleep time, sleepiness and pain began in chronic pain patients. A Wayne State University (WSU) PhD clinical psychology student, Mazy Gillis, heard a talk of mine on sleep and sleepiness and approached me regarding adding a self-report sleep assessment to her dissertation. Her dissertation assessed the health effects of at-home written emotional disclosure in people with fibromyalgia [26]. I was not familiar with the sleep-pain literature and searched that literature which led to a review paper on this new research area for me [27]. In Dr. Gillis' dissertation results one of the stronger positive health effects of emotional disclosure was a reduction in sleep problems. This led to Dr. Gillis' interest in the role of sleep problems in chronic pain. Dr. Gillis then wrote a proposal and was awarded a three-year post-doctoral fellowship by the Arthritis Foundation. The study tested whether the sleep problems of fibromyalgia were due to homeostatic sleep mechanism dysfunction or hyperarousal as shown in people with insomnia disorder. The study compared the PSG sleep and MSLT defined daytime sleepiness in healthy volunteers, people with arthritis and with fibromyalgia after 8 hours and 4 hours TIB and followed by 8 hours recovery TIB [28]. The MSLT and recovery sleep results in the fibromyalgia group were like those of the healthy volunteers, suggesting that homeostatic sleep mechanisms in fibromyalgia were normally responsive.

A WSU Psychiatry colleague, Dr. Mark Greenwald, heard of my new interest in sleep and pain and gave me a home-made pain assessment device. The device measures finger withdrawal latency (FWL) to a radiant heat stimulus, presented at five different heat intensities in a random order. The value of the methodology is it provides an internal validation of the pain assessment for a given experiment, such that in the basal or placebo condition low heat intensities should be related to longer FWL and high-intensities with short FWL. In a further validation MSLT-defined sleepy (MSLT < 8 minutes) and non-sleepy volunteers (MSLT > 8 minutes) were studied [29]. They received placebo or codeine 30 mg bid (0900 & 1300 hours). Codeine increased FWL (the expected analgesic effect) in the non-sleepy individuals, *but not* in the sleepy individuals. These results further validated the FWL methodology, but also showed clinical differences in response to analgesics could be partly explained by the person's basal state of sleepiness-alertness.

Because the sleepy vs non-sleepy differences in pain sensitivity previously shown above may be due to other factors beyond the participants sleepy state, we sought to create sleepiness in healthy, normally alert individuals by restricting TIB and assessing TIB effects on pain sensitivity. Further, the role of REM sleep in analgesia is unclear and we sought to assess the impact of REM deprivation on pain sensitivity. In a repeated measure study healthy volunteers underwent FWL testing after 8 hours and 4 hours TIB and after REM deprivation versus non deprivation yoked control nights [30]. After 4 hours sleep loss FWL was reduced by 25% relative to 4 hours TIB and by 32% after REM deprivation relative to a non-REM yoked awakening control condition.

While these studies showed the relation of sleep loss/sleepiness to pain sensitivity, the compelling clinical question is whether improved sleep is associated with reduced pain sensitivity. Healthy adults with mild sleep loss and a MSLT sleep latency of< 8 minutes were randomized to four nights of 10 hours TIB (EXT) or 4 nights of their habitual sleep schedule (HAB) with MSLT and FWL testing each day [31]. The EXT group nightly slept 1.8 hours more than the HAB group and their MSLT by EXT day 4 had increased by 50%. Finger withdrawal latency increased (lessened pain sensitivity) in the EXT group but not the HAB group.

We then applied our sleep extension methods to clinical situations. First, among patients undergoing knee or hip replacement we recruited patients who reported sleeping 6.5 hours or less nightly [32]. For the week before surgery, they were randomized to a 10 hours TIB extension or remained on their habitual bedtime schedule. During the three post-surgery inpatient days we monitored their self-reported pain and narcotic medication use as a marker of pain sensitivity. For the pre-surgery week the EXT group nightly slept 1 hour more than the HAB group. On the three inpatient post-surgery days the EXT group reported less daily pain and used 30% less narcotic medication than the HAB group Patients with OSA are known to have fragmented sleep and PAP treatment reduces the number of apneas and consolidates sleep. On the morning after a patient's diagnostic night those with severe OSA were recruited to undergo FWL testing [33]. PAP pressure was titrated on a second night in the laboratory and two nights after titration, patients returned to sleep in the laboratory on their prescribed PAP pressure. FWL was again tested in the morning. Finger withdrawal latency increased (i.e. reduced pain sensitivity) relative to baseline after the PAP treatment nights. After six weeks at home remaining on their prescribed PAP pressure patients returned to sleep in the lab without the PAP treatment and in the morning FWL returned to baseline pretreatment levels (i.e., the analgesic benefit of non-fragmented sleep due to the PAP) was lost. I am most proud of these sleep and pain studies as they make an important contribution to medical practice. I was amazed that merely one-hour improvements in sleep time and sleep continuity would reduce pain sensitivity and analgesia use.

Openness to critique and advice

My successful sleep research career would not have been possible without the advice and critique of many colleagues. Primarily, Tom Roth, initially my mentor and later a colleague, has provided incredibly helpful ideas, advice, and critique throughout my career. He served as a Co-Investigator on many of my grants and projects. Then there are the numerous students, fellows, research assistants, associates, and coordinators that did the day-to-day work. I also relied on the SD&RC medical directors, Drs Frank Zorick, Leon Rosenthal, David Hudgel, and Luisa Bazan who over the years resolved the various medical questions I encountered.

It was my openness and inquisitiveness, learned early in my career, which has led to my broad contribution to sleep science.

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