A double-blind, cross-over, study to compare the hypnotic, daytime sleepiness/fatigue, and pain effects of nighttime administration of suvorexant 20 mg versus placebo in patients with fibromyalgia and comorbid insomnia.

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2.1 Objectives and Hypotheses

2.1.1 The primary objectives of this proposed study in persons with fibromyalgia and co-morbid insomnia are:

1) to assess the effect of suvorexant 20 mg versus placebo on polysomnographic (PSG) measures of sleep.

2) to assess the effect of suvorexant 20 mg versus placebo on next day measures of sleepiness/fatigue.

3) to assess the effect of suvorexant 20 mg versus placebo on next day measures of nociception and pain.

2.1.2 The clinical hypotheses to be tested are:

1) relative to placebo suvorexant 20 mg will increase PSG sleep efficiency and reduce sleep latency and wake after sleep onset in persons with fibromyalgia and comorbid insomnia.

2) relative to placebo suvorexant 20 mg will reduce self-reported next-day pain and nociceptive sensitivity as measured by Finger Withdrawal Testing (FWT) in persons with fibromyalgia and comorbid insomnia.

3) relative to placebo suvorexant 20 mg will reduce self-reported next-day fatigue and normalize Multiple Sleep Latency Test (MSLT) scores in persons with fibromyalgia and comorbid insomnia.

2.2 Background and Rationale

Typically insomnia is co-morbid with various medical and psychiatric disorders and among the disorders frequently co-morbid with insomnia are the various chronic pain disorders. A prevalent musculoskeletal chronic pain disorder is fibromyalgia in which pain is widespread and not specifically localized (1). Its etiology is unknown, although a prominent hypothesis suggests the pain is associated with enhanced central nervous system sensitization shown over all sense modalities (2). Between 60-80% of fibromyalgia patients complain of sleep disturbance, which most typically is a sleep maintenance problem, a complaint which has been confirmed with polysomnography (PSG). Another important persisting symptom in fibromyalgia is daytime sleepiness and fatigue, which may relate to the disturbed sleep of fibromyalgia or the underlying pathophysiology of the disorder, putative pro-inflammatory cytokine activation.

The PSG studies in fibromyalgia, dating to as early as 1975, have consistently reported reduced total sleep time relative to age-matched controls, primarily due to increased wake time after sleep onset (WASO) (3). However, despite having reduced nocturnal sleep compared to

age-matched healthy controls and reporting elevated levels of daytime sleepiness and fatigue like patients with rheumatoid arthritis, patients with fibromyalgia show elevated daytime arousal on an objective measure of daytime sleepiness/alertness, the Multiple Sleep Latency Test (MSLT) (4). Elevated MSLT latencies, despite shorter total sleep times, have also been seen in people with primary insomnia, which is consistent with the sensory hypersensitization model of fibromyalgia (2).

It has now become clear that the relation of sleep and pain is bidirectional; acute and chronic pain are associated with disturbed sleep and shortened and disturbed sleep enhances pain. Experimental studies have shown that reduced and fragmented sleep in pain-free normals increases their pain sensitivity and daily self-report studies in chronic pain patients have shown a poor night of sleep is followed by enhanced next-day pain (3). In mediation analyses of large clinical data sets it is found that the sleep-pain side of the bidirectional relation, as opposed to the pain-sleep side, accounts for the greater variance (5). These data then would suggest that improving sleep in chronic pain disorders should attenuate daytime pain.

Drugs from a number of different drug classes have been assessed as treatments in chronic pain disorders including analgesics, antidepressants, antiepileptics, and hypnotics. In many of these studies pain is the major study focus and if sleep is measured, it is a secondary outcome and typically only measured by self-report. Further, rarely are patients in these studies specifically included for the presence of co-morbid insomnia and degree of sleep disturbance.

While analgesics, antidepressants, and antiepileptics are typically used and studied in chronic pain disorders, only a few studies have assessed hypnotics and with quite mixed results. In fibromyalgia patients zolpidem (6), but not zopiclone (7), improved some of the sleep measures, but neither drug improved pain. Triazolam improved sleep and pain in patients with rheumatoid arthritis (8), whereas zopiclone only improved pain (9). A large (N=153) study of eszopiclone, the S isomer of zopiclone, assessed its sleep and pain effects in patients with insomnia co-morbid with rheumatoid arthritis (10). Eszopiclone compared to placebo improved self-reported measures of sleep and most all of the pain measures. Hospitalized patients with mucositis associated with chemotherapy for hematologic malignancies were randomized to 2 nights of eszopiclone or placebo (11). Pain scores throughout the day were improved with eszopiclone and patients reported increased sleep time and fewer awakenings.

Most of the drugs used to treat chronic pain facilitate inhibitory CNS mechanisms as their primary mechanism of action. Suvorexant, recently approved by the FDA for the treatment of insomnia characterized by difficulties with sleep onset and sleep maintenance, has a unique mechanism of action. Suvorexant is a selective antagonist for orexin receptors (OX1R and

OX2R) (12). Orexins are considered to be involved in arousal and maintenance of the waking state. In support of this view, findings have shown that orexin neurons send dense projections to brain arousal areas including the locus coeruleus, tuberomammillary nucleus, and the basal forebrain cholinergic system (13). In PSG studies in healthy men, suvorexant 10 mg increased sleep efficiency and reduced WASO (14) and in patients with primary insomnia it increased sleep efficiency by reducing latency to persistent sleep (10 min of continuous sleep) and WASO (15).

As such, suvorexant may provide unique clinical benefit as a treatment in chronic pain conditions with co-morbid insomnia, and specifically for fibromyalgia with its putative central hyperarousal and hypersensization. Thus, this project proposes to study objective and clinical measures of sleep, pain, and daytime sleepiness and fatigue in patients with fibromyalgia and co-morbid insomnia while treated short-term with suvorexant 20 mg versus placebo.

2.3 Study Design

The study will be conducted as a double blind, placebo controlled, trial using a repeated measures design. Patients with fibromyalgia and co-morbid insomnia (n=30) will be treated for 9 nights each with suvorexant 20 mg and placebo with the order of treatments counterbalanced. The study will be registered on clinicaltrials.gov

2.4 Study Flowchart

Patients with fibromyalgia and co morbid insomnia will be recruited from the HFHS hospitals and clinics and from patient support groups in Metro Detroit. In our most recent study of fibromyalgia we were able to recruit 20 patients over a period of twelve months. Patients will be assessed clinically for fibromyalgia and insomnia using American College of Rheumatology (ARC) (16) and Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (17) criteria, respectively. They will be screened by PSG for other primary sleep disorders and a sleep efficiency (sleep time/bedtime) of $\leq$ 85%.

2.4.1 Inclusion Criteria

- Women with good psychiatric and stable physical health.
- Aged between 21 and 65 yrs old.
- Having a customary bedtime of 12 midnight or earlier, having at least 6 to 8 hrs in bed on average.
- Meeting the American College of Rheumatology criteria for fibromyalgia.
- Having wide spread pain, which includes pain in all four quadrants; including symptoms and/or complaints of fatigue, waking non-refreshed and cognitive symptoms.
- Current average pain severity score $\geq$ 4 on the Brief Pain Inventory at screening.
- Meeting the Diagnostic and Statistical Manual of Mental Disorders, fifth edition, criteria for insomnia and additionally with a sleep efficiency of $\leq$ 85% on a screening PSG.

2.4.2 Exclusion Criteria

- Pain symptoms (unrelated to fibromyalgia) that could interfere with the interpretation of outcome measures; regional pain syndromes (eg. back, neck); multiple surgeries; pain from a traumatic injury; a confirmed current or previous diagnosis of rheumatoid arthritis, or similar disorders, inflammatory arthritis, or other autoimmune disease, osteoarthritis, tendonitis, unstable medical or psychiatric disorders.
- Any condition that could confound assessment of sleep, including depression (scoring 14 ≥ on the Hamilton Depression Rating Scale (HAM-D), anxiety (scoring 24≥ on the Hamilton Anxiety Rating Scale (HAM-A), other psychiatric disorders, chronic medical conditions (e.g. liver disease, heart failure) or uncontrolled medical conditions.
- Consuming >14 alcoholic beverages per week (and/or >5 or > 4 drinks per single occasion for males and females, respectively) and >300mg of caffeine per day.
- The inability to discontinue, hypnotics or antidepressants.
- Substance abuse within the last 2 years and/or a failed urine drug screen;
- Primary sleep disorders, including narcolepsy, or circadian rhythm sleep disorder, excluding insomnia;
- Respiratory disturbances [apnea hypopnea index] or periodic limb movement arousal index greater than 10 per hour of sleep.
- Having a history of frostbite and/or Raynaud's syndrome.
- Current pregnancy or breast-feeding.

While patients will be told to discontinue hypnotic use, they will be allowed use of pain medications throughout the study to be recorded in a daily diary, as long as they are using a stable dose on a regular basis. The one exception will be that sedating tricyclic antidepressant use will be excluded. Patients will be asked to discontinue their antidepressant or hypnotic use two weeks before entering the study protocol.

Those qualifying will receive suvorexant 20 mg and placebo for each of 9 nights in a cross over design with 7 nights of washout between treatments. PSGs will be collected on nights 7 and 8 of each crossover treatment arm. During day 8 of each treatment a MSLT (1000, 1200, 1400, and 1600 hr) will be done, and on days 1 and 8 nociceptive sensitivity [finger withdrawal latency (FWL)] testing to a radiant heat stimulus (1100 and 1500 hr) will be conducted. On days 1 and 8 self-reported mood and pain indices will also be completed prior to each nociceptive sensitivity test.

2.5 Study Procedures

2.5.1 Polysomnography (PSG)

For each PSG night, participants will arrive 2 hours prior to their reported bedtime to complete check-in procedures and undergo electrode placement for standard 8-hr PSGs (18). Bedtimes will be determined using the participant's self-reported normal sleep schedule with

time in bed fixed to 8 hrs. For the screening PSG, central and occipital electro-encephalogram (EEG) leads (C3-A2 and O2-A1) will be placed to measure EEG activity and left and right horizontal electroculograms (EOG) will be used to measure eye movements. A V5 electrocardiogram (ECG) lead and a sub-mental electromyogram (EMG) lead will be placed. Airflow (by pressure transducer), body position via video recording, thoracic and abdominal excursion (inductance plethysmography), oxygen saturation (finger pulse oximetry), leg movement (with electrode over left anterior tibialis muscle), and sound will also be recorded. For the study nights 8 and 9 the 8-hr PSGs will consist of continuous monitoring of two channels of EEG (C3-A2 and O2-A1), left and right EOGs, submental EMG and V5 ECG.

All recordings will be scored in 30 second epochs for standard sleep stages according to the standards of Rechtschaffen & Kales (18). Scoring will be done by technicians with established intra-laboratory scoring concordance and verified by review of the PI or CoI. Respiratory events and periodic leg movement events will be scored according to established AASM published criteria (19). Based on the screening PSG, patients with respiratory or periodic leg movement event indices of > 10 will be excluded.

2.5.2 Daytime Sleepiness/Alertness (MSLT)

Each test of the MSLT will be conducted according to the standard research MSLT protocol (20). Participants will be placed in bed in quiet, darkened rooms and instructed to close their eyes, relax, and fall asleep. Each test is concluded after 20 minutes of continuous wake or after three continuous 30s epochs of stage one sleep, or one epoch of any other sleep stage. Latency to sleep onset will be scored as min to the first epoch of sleep or 20 min if sleep did not occur. The latencies for the 4 tests are averaged to generate a single latency value.

2.5.3 Nociceptive Sensitivity (FWL)

A radiant heat method will be used to assess nociceptive sensitivity (21). Participants are seated in a comfortable chair at a desk with their hand resting on top of a metal box housing the heat source. The pad of the index finger (fingerprint whorl) is centered over a 3-mm hole

through which the heat radiates. The heat source is a 100-watt projection bulb, located 10 mm from the finger. A potentiometer controls the amount of current delivered to the light bulb, thereby varying heat intensity. On each trial, participants are instructed to place their index finger on the hole through which the heat source radiates and to withdraw their index finger when they first began to feel pain. Once finger withdrawal occurs, a photocell (mounted on a post located above the finger) detects the light (from the bulb underneath) and stops a digital timer connected to the circuit. Both index fingers are tested and the heat intensities are adjusted on each trial such that five different heat intensities (ranging from 83.4 to 101.6 degrees Fahrenheit, measured at steady-state after 10-sec duration) are presented in a randomized order. The FWL from left and right index fingers are averaged. The primary dependent measure is mean FWL (to a resolution of 0.01 sec) for each of the 5 heat intensities.

Patients initially will undergo a training session to familiarize themselves with the nociceptive testing equipment and procedures. The threshold at which a finger withdrawal response is elicited for each participant is established. The threshold radiant heat intensity is defined as the intensity that produces FWL of <21 sec.

As to the validity of the radiant heat method, our studies have shown FWL is systematically related to stimulus intensity (greater intensity = shorter FWL), basal level of sleepiness/alertness (greater sleepiness = shorter FWL), and codeine versus placebo (codeine = longer FWL) (21). Importantly, in healthy normals without sleep disturbance reducing sleep time by as little as 2 hrs reduces FWL and increasing sleep time by as little as 1 hr increases FWL (22,23). Further, in patients with moderate to severe obstructive sleep apnea (OSA) treated with Continuous Positive Airway Pressure (CPAP), thereby eliminating the OSA and consolidating sleep, FWL is increased and when the CPAP is discontinued for two nights FWL is again reduced (24).

2.5.4 Morning Self-reported Sleep and Previous Day Pain Assessment

Each morning after arising participants will complete a brief questionnaire regarding the previous night's sleep and the previous day's pain. The Red Cap questionnaires will be

accessed over the internet by participants' using their own password protected login identification credential with a daily time-limited completion interval (before 12 noon each day). The questionnaire will query regarding latency to fall asleep, wake time after falling asleep, total sleep time, pain disruption of sleep and alertness after awakening in the morning. Daytime pain the previous day will be assessed using the Short-Form McGill Pain Questionnaire (28).

2.5.5 Safety Monitoring

Each participant will complete the Columbia Suicidality Scale at screening and on study day 1 and 8. Additionally the Hamilton Depression Rating Scale (HAM-D) and Hamilton Anxiety Rating Scale (HAM-A) will also be completed on those days. The rating scales will be administered between the first and second nociceptive sensitivity testing (at approximately 1130 hr) on each day. Changes on any of these scales from the scores established at the baseline will be reported as AEs (see below). On day three of each of the treatment periods the patient/subjects will be contacted by phone to determine whether they are experiencing AEs.

2.6 Study Duration

It is estimated that the study can be completed within 18 months and that data analysis and paper preparation can be completed in an additional six months.

2,7 Statistical Procedures and Sample Size Justification

2.7.1 Statistics

The primary PSG efficacy variables will be sleep efficiency and WASO computed as a mean of nights 7 and 8. The secondary PSG measures will include nocturnal sleep latencies and sleep stages. The primary daytime measures will be the MSLT scores from day 8 and the FWL test results (the average of the am and pm tests) from day 1 and day 8. Secondary daytime measures will include the in-lab self-ratings of sleepiness/fatigue and pain. Another set of secondary measures will be the morning ratings of sleep and previous day's pain collected on the internet administered questionnaires during each 9 day treatment condition. The in-lab sleep, daytime sleepiness/fatigue, and pain data for each dependent variable of the two 9 day conditions will be compared using two factor MANOVAs with drug (suvorexant vs placebo) and days (7 and 8) as the two repeated factors. The internet questionnaire data will be treated similarly using drug and days as two repeated measures. In addition we will conduct path

analyses to determine the degree to which the change in nociceptive sensitivity is mediated directly by suvorexant and indirectly by suvorexant's effect on sleep.

2.7.2 Sample Size

Our estimates of necessary sample size and the associated powers are presented in Appendix A. The sample sizes and associated powers are presented for each of the primary outcome measures. Given these assessments, we have chosen to recruit 30 patients.

2.8 Drug Supply Requirements

Nine nights each of suvorexant 20 mg and matching placebo will be required for each participant with the total study sample being 30. (270 suvorexant 20 mg and 270 placebo). In addition accounting for a 10% dropout rate we anticipate a total need for 300 20 mg suvorexant and 300 placebos

2.9 Adverse Event Reporting

Adverse events (AE) will be collected and reported to the study sponsor and the HFHS IRB as blinded events quarterly. Serious adverse events (SAEs) will be reported as unblinded events to the study sponsor, the HFHS IRB and the FDA. SAEs will be reported within 48 hrs of becoming aware of the event. Initial reports will be followed by reports of the resolution of the SAE.

2.10 References

1) Wolfe F, Clauw DJ, Fitzcharles MA, et al. The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. Arthritis Care Res. 2010;62:600-610.

2) Ynus, M. B. Fibromyalgia and overlapping disorders: The unifying concept of central sensitivity syndromes. Seminars in Arthritis and Rheumatology, 2007;36:339-356.

3) Roehrs T, Roth T. Pain and sleep. In: Babson KA, Feldner MT (eds). Sleep and Affect. New York: Elsevier, 2015, pp 377-397.

4) Roehrs T, Diederichs C, Gillis M, Burger AJ, Stout RA, Lumley MA, Roth T. Nocturnal sleep, daytime sleepiness and fatigue in fibromyalgia patients compared to rheumatoid arthritis patients and healthy controls: A preliminary study. Sleep Med 2013;14:109-115.

5) Russel,I. J., Crofford, L. J., Leon, T., Cappelleri, J. C., Bushmakin, A. G., Whalen, E., Barrett, J. A., & Sadosky, A. The effects of pregabalin on sleep disturbance symptoms among individuals with fibromyalgia syndrome. Sleep Med 2009;10:604-610.

6) Moldofsky H, Lue FA, Mously C, Roth-Schechter B, Reynolds, WJ. The effect of zolpidem in patients with fibromyalgia: a dose ranging, double-blind, placebo controlled, modified crossover study. J Rheumatol 1996; 23:529-533.

7) Gronbald, M., Nykanen, J., & Konttinen, Y. Effect of zolpiclone on sleep quality, morning stiffness, widespread tenderness and pain and general discomfort in primary fibromyalgia patients. A double-blind randomized trial. Clin Rheumat 1993;12:186-191.

8) Walsh, J. K., Muehlbach, M. J., Lauter, S. A., Hilliker, A., & Schweitzer, P. K. Effects of triazolam on sleep, daytime sleepiness, and morning stiffness in patients with rheumatoid arthritis. J Rheumat 1996;23:245–252

9) Drewes, A. M., Bjerregard, K., & Taaghold, S. J. Zopiclone as night medication in rheumatoid arthritis. Scan J Rheumat 1998;27:180-187.

10) Roth, T., Lankford, A., Bhadra, P., Whalen, E., & Resnick, E. M. Effect of pregabalin on sleep in patients with fibromyalgia and sleep maintenance disturbance: A randomized, placebo-controlled, 2-way crossover polysomnography study. Arthritis Care Res 2012;62:597-606.

11) Dimsdale, J. E., Ball, E. D., Carrier, E., Wallace, M., Holman, P., Mulroney, C., Shaikh, F., & Natarajan, L.. Effect of eszopiclone on sleep, fatigue, and pain in patients with musocitis associated with hematologic malignancies. Support Care Cancer 2011;19:2015-2020.

12) Hoyer D, Jacobson LH. Orexin in sleep, addiction and more: Is the perfect insomnia drug at hand. Neuropeptides 2013;47:477-488.

13) Harris GC, Aston-Jones G. Arousal and reward: a dichotomy in orexin function. TINS 2006;29:571-577.

14). Sun H, Kennedy WP, Wilbraham D, Lewis N, Calder N, Li X, Ma J, Yee KL, Ermlich S, Mangin E, Lines C, Rosen L, Chodakewitz J, Murphy GM. Effects of suvorexant, an orexin receptor antagonist, on sleep parameters as measujred by polysomnography in healthy men. Sleep 2013;36:259-267.

15) Herring WJ, Snyder E, Budd K, Hutzelmann J, Snavely D, Liu K, Lines C, Roth T. Michelson D. Orexin receptor antagonism for treatment of insomnia. Neurology 2012;79:2265-2274.

16) Wolfe F. Fibromyalgia. Rheum Dis Clin North Am. 1990;16:681-698.

17) American Psychiatric Association. Diagnostic and statistical manual of mental disorders, Fifth Ed. (DSM-5), Washington DC: American Psychiatric Association, 2013.

18) Rechtschaffen A, Kales A, eds. A manual of standardized terminology, techniques and scoring system for sleep stages of human subjects. Los Angeles, CA: UCLA Brain Information Service/Brain Research Institute, 1968.

19) Berry RB, Brooks R, Gamaldo CE, Harding SM, Lloyd RM, Marcus CL, Vaughn BV. The AASM manual for the scoring of sleep and associated events. Darien, IL: American Academy of Sleep Medicine, 2014.

20) Carskadon MA, Dement WC, Mitler MM, Roth T, Westbrook PR, Keenan S. (1986). Guidelines for the Multiple Sleep Latency Test (MSLT): A standard measure of sleepiness. Sleep, 1986;9:519-524.

21) Chhangani BS, Roehrs TA, Harris EJ, Hyde M, Drake C, Hudgel DW, Roth T. Pain sensitivity in sleepy pain-free normals. Sleep 2009;32:1011-1017.

22) Roehrs, T. A., Hyde, M., Blaisdell, B., Greenwald, M., & Roth T. Sleep loss and REM sleep loss are hyperalgesic. Sleep 2006; 29:145-151.

23) Roehrs TA, Harris E, Randall S, Roth T. Pain sensitivity and recovery from mild chronic sleep loss. Sleep 2012;35:1602-1608.

24) Khalid I, Roehrs TA, Hudgel DW, Roth T. Continuous positive airway pressure in severe obstructive sleep apnea reduced pain sensitivity. Sleep 2011;34:1687-1691.

25) Okura K, Lavigne GJ, Huynh N, Manzini C, Fillipini D, Montplaisir JY. Comparison of sleep variables between chronic widespread musculoskeletal pain, insomnia, periodic leg movements syndrome and control subjects in a clinical sleep medicine practice. Sleep Medicine 2008;9:352-361.

26) Hindmarch I, Dawson J, Stanley N. A double-blind study in healthy volunteers to assess the effects on sleep of pregabalin compared with alprazolam and placebo. Sleep 2005;28:187-193.

27) Stout R, Burger A, Villareal A, Gillis M, Lumley M, Roehrs T, Roth T. Objective sleepiness following sleep restriction in rheumatoid arthristis and fibromyalgia. Sleep 2007;30:A323 (ab).

28) Hawker GA, Mian S, Kendzerske T, French M. Measures of adult pain. Arth Care & Res 2011;63:S240-S252.

2.12 Publication Plan

The PI and CoI will be responsible for analyses and paper preparation. The paper will submitted to the study sponsor Merck for approval prior to submission for publication.

APPENDIX A

Sample Size and Power Estimates

All estimates based on two-tailed tests with alpha set at 0.05

Nocturnal Polysomnographic (NPSG) Sleep Efficiency (SE)

Based on a SE increase of 8% versus placebo with 20 mg suvorexant in primary insomnia (Herring et al, Neurology 2012;79:2265-2273).

Paired t-test with Alternative 'not equal'

Expected Difference	:	8.000
Standard Deviation of Difference	:	12.800
Effect Size	:	0.625
ALPHA	:	0.050
Sample Size: Low	:	20
Sample Size: High	:	30
Increment	:	1

Sample Size (Per Cell)	POWER
20	0.755
21	0.778
22	0.798
23	0.817
24	0.834
25	0.850
26	0.865
27	0.878
28	0.890
29	0.901
30	0.911

Based on a SE increase of 6% versus placebo with 10 mg zolpidem in primary insomnia (Randall et al, Sleep 2012;35:1551-1557).

Paired t-test with Alternative 'not equal'

Expected Difference	:	6.000
Standard Deviation of Difference	:	9.000
Effect Size	:	0.667
ALPHA	:	0.050
Sample Size: Low	:	20
Sample Size: High	:	30
Increment	:	1

Sample Size (Per Cell)	POWER
20	0.807
21	0.828
22	0.846
23	0.863
24	0.878
25	0.892
26	0.904
27	0.915
28	0.925
29	0.934
30	0.942

Sample Size and Power Estimates

All estimates based on two-tailed tests with alpha set at 0.05

Nocturnal Polysomnographic (NPSG) Wake after Sleep Onset (WASO)

Based on a WASO reduction of 25 min versus placebo with 20 mg suvorexant in primary insomnia (Herring et al, Neurology 2012;79:2265-2273).

Paired t-test with Alternative 'not equal'

Expected Difference	:	25.000
Standard Deviation of Difference	:	45.000
Effect Size	:	0.556
ALPHA	:	0.050
Sample Size: Low	:	20
Sample Size: High	:	30
Increment	:	1

Sample Size (Per Cell)	POWER
20	0.655
21	0.678
22	0.700
23	0.721
24	0.741
25	0.760
26	0.777
27	0.794
28	0.809
29	0.823
30	0.837

Based on a WASO reduction of 20 min versus placebo with 10 mg zolpidem in primary insomnia (Randall et al, Sleep 2012;35:1551-1557).

Paired t-test with Alternative 'not equal'

Expected Difference	:	20.000
Standard Deviation of Difference	:	43.000
Effect Size	:	0.465
ALPHA	:	0.050
Sample Size: Low	:	20
Sample Size: High	:	30
Increment	:	1

Sample Size (Per Cell)	POWER
20	0.506
21	0.527
22	0.548
23	0.569
24	0.588
25	0.607
26	0.625
27	0.643
28	0.660
29	0.677
30	0.692

Sample Size and Power Estimates

All estimates based on two-tailed tests with alpha set at 0.05

Multiple Sleep Latency Test (MSLT)

Based on reduction in MSLT in Fibromyalgia patients following 1 night of 4 hrs time in bed (i.e. reflects sensitivity of MSLT to sleep time manipulations) relative to their baseline “hyperaroused” MSLT (Roehrs et al, J Psychosom Res 2015:79:27-31)

Paired t-test with Alternative 'not equal'

Expected Difference	:	4.300
Standard Deviation of Difference	:	4.800
Effect Size	:	0.896
ALPHA	:	0.050
Sample Size: Low	:	20
Sample Size: High	:	30
Increment	:	1

Sample Size (Per Cell)	POWER
20	0.967
21	0.974
22	0.979
23	0.984
24	0.987
25	0.990
26	0.992
27	0.994
28	0.995
29	0.996
30	0.997

Based on increase in MSLT in “sleepy” volunteers after 4 nights of 1 hr increased sleep per night (Roehrs et al, Sleep 2012;35:1667-1672)

Paired t-test with Alternative 'not equal'

Expected Difference	:	4.500
Standard Deviation of Difference	:	3.800
Effect Size	:	1.184
ALPHA	:	0.050
Sample Size: Low	:	20
Sample Size: High	:	30
Increment	:	1

Sample Size (Per Cell)	POWER
20	0.999
21	0.999
22	1.000
23	1.000
24	1.000
25	1.000
26	1.000
27	1.000
28	1.000
29	1.000
30	1.000

Finger Withdrawal Latency (FWL)

Based on increase in FWL (i.e. reduction in pain sensitivity) in “sleepy” volunteers after 4 nights of 1 hr increased sleep per night (Roehrs et al, Sleep 2012;35:1667-1672

Paired t-test with Alternative 'not equal'

Expected Difference	:	2.600
Standard Deviation of Difference	:	2.500
Effect Size	:	1.040
ALPHA	:	0.050
Sample Size: Low	:	20
Sample Size: High	:	30
Increment	:	1

Sample Size (Per Cell)	POWER
20	0.993
21	0.995
22	0.996
23	0.997
24	0.998
25	0.999
26	0.999
27	0.999
28	1.000
29	1.000
30	1.000

Estimating greater variability in a Fibromyalgia sample

Paired t-test with Alternative 'not equal'

Expected Difference	:	2.600
Standard Deviation of Difference	:	3.500
Effect Size	:	0.743
ALPHA	:	0.050
Sample Size: Low	:	20
Sample Size: High	:	30
Increment	:	1

Sample Size (Per Cell)	POWER
20	0.883
21	0.899
22	0.913
23	0.926
24	0.936
25	0.945
26	0.953
27	0.960
28	0.966
29	0.971
30	0.976