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MD Anderson Cancer Center

Protocol Page

A pilot open label study to investigate the role of lenalidomide in improving cancer related sleep in CLL patients over 65 years of age experiencing clinically significant fatigue
2007-0945

Core Protocol Information

Short Title	A pilot study to investigate the effect of cytotoxic therapy and/or radiotherapy on cancer related sleep disturbances in CLL and breast cancer patients experiencing fatigue
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Which Committee will review this protocol?

(●) The Clinical Research Committee - (CRC)

Protocol Body

1.0 Background

Background: CLL is the most prevalent leukemia found in adults in Western countries. CLL is common among the elderly and more than half of the patients are seventy years or older at the time of their diagnosis. These elderly CLL patients have severe sleep disturbances and CRF. Older patient are more likely to experience frequent and severe symptoms than younger patients (1, 7).

(a) CLL and cancer related symptoms - In a longitudinal study to determine the long-term QOL of patients with CLL, 97 patients with CLL were asked to complete the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) four times over a period of one year. Compared with healthy age matched controls, CLL patients reported a lower QOL in almost all domains. No differences regarding QOL could be observed between CLL patients who had already received chemotherapy and those who had not. Female CLL patients reported a substantially lower QoL in each of the EORTC QLQ-C30 Functioning Subscales, with effect sizes ranging from small (0.35, cognitive functioning) to large (1.04, physical functioning). Fatigue, sleep disturbance, nausea/vomiting, appetite loss, and constipation were significantly more common in patients with CLL than in the controls. Patients suffering from CLL-associated symptoms could have their QoL improved by alleviation of these severe symptoms(1,7).

(b) **CLL and fatigue** – One of the more frequent complaints of CLL patients is fatigue(1,7). Patients often describe themselves as drained from energy and require multiple rest periods during the day to perform their activities. This reduced energy appears to not be related to the stage of the disease as it is commonly found in the early phase of this leukemia and appears to be more noticeable in women. Perhaps related to fatigue, patients with CLL will often complain of difficulties in concentration and in performing complex tasks. The exact cause of this symptom is unknown. At present, there are limited treatment options for fatigue and fatigue-related symptoms in patients with CLL.

(c) **Role of sleep in the causation of fatigue:** although cancer-related fatigue and cancer-related sleep disorders are distinct, a strong interrelationship exists between these symptoms, with a strong possibility that they may be directly associated. The majority of studies that have assessed both sleep and fatigue in patients with cancer provide evidence supporting a strong correlation between cancer-related fatigue and various sleep disorders, including poor sleep quality, disrupted initiation and maintenance of sleep, nighttime awakening, restless sleep, and excessive daytime sleepiness(2-6). Following a review of the epidemiology of insomnia in patients with cancer, Savard and Morin concluded that insomnia disorder added a additional risk for experiencing intense and persistent fatigue after cancer treatment(5).

d) **Fatigue and Cytokines**: Tumor necrosis factor-alpha (TNF-á), interleukin (IL)-1 â, IL-8, IL-10 and IL-6 have been implicated in the pathophysiology of fatigue, acting in multiple domains including mood, muscle mass, strength, and metabolic status (6-8). Immunotherapies, such as interferon-alpha (IFN-á), IL-2, and TNF-á have been associated with symptoms of fatigue, mood swings, sleep disturbance, and cognitive changes (10, 11). Cytokine-associated symptoms such as anorexia, cachexia, chronic nausea, fever, depression, pain, and sleep disorders may also contribute to fatigue (12-18).

(e) **Sleep and Cytokines**: The literature regarding cytokines and sleep highlights the role of at least two cytokines IL-1 â and TNF-á in the regulation of sleep. Both cytokines can enhance slow wave NREM sleep, perhaps as a result of changes in cytoplasmic Ca2+ uptake/flux in the hypothalamus. IL-1â may also affect the serotonergic pathway to increase NREM sleep. Human subjects on IL-1â therapy often complain of fatigue and sleepiness. Recent studies suggest that IL-6 may be involved in the alteration of sleep, especially during illness. Under normal circumstances IL-6 in plasma exhibits a diurnal rhythm with peak values during sleep and nadirs during wakefulness. Sleep deprivation of human subjects increases IL-6 as well as subcutaneous injection of IL-6 increased slow wave sleep and decreased REM sleep of humans. Genetically manipulated IL-6 deficient mice have increase REM sleep and are more resistant to sleep deprivation (17). Patients with cancer, who are undergoing cancer therapy, experience significant alterations in their cytokine levels. These patients also experience the disabling symptoms of fatigue and sleepiness. Recent evidence suggests the role of inflammatory cytokines IL-1â, TNF- á, IL-8, IL-10 and IL-6 in the etiology of cancer related symptoms such as fatigue and sleep disturbance (6, 18).

(f) **CLL and inflammatory cytokines:** CLL cells are capable of producing several cytokines that suppress the function of normal T cells and inhibits apotosis of B-CLL cells. It has been shown that CLL cells release TNF- in vitro and exposure to TNF- increases their proliferation and viability. We previously reported that patients with CLL have significantly higher plasma concentrations of TNF- than the healthy control population and that patients with higher levels of TNF- had more advanced disease and significantly shorter survival (19). In general, pro-inflammatory cytokines promote sleep whereas anti-inflammatory cytokines suppress sleep. Patients with CLL also have increased levels of anti-inflammatory cytokines, IL-4 and IL-10 (20), that are likely to contribute to symptoms and sleep disturbances.

(g) **Lenalidomide for the treatment of other cancer-related symptoms:** Thalidomide and similar compounds such as IMiDs have demonstrated benefit by relieving symptoms such as sleep disturbance, anorexia and nausea in cancer patients. These symptoms are known contributors to cancer related fatigue. However, due to its side-effect profile including sedation, its clinical application has been limited. An IMiD such as Lenalidomide is able to induce clinical responses in 34-48% of patients with relapsed/refractory CLL and also has decreased symptomatic neurological side effect profile as compared to thalidomide (8,21). Since lenalidomide has shown efficacy in patients with refractory CLL accompanied by reductions in plasma IL-6 and TNF-á levels (8), we decided to investigate whether lenalidomide will affect sleep and fatigue in elderly CLL patients (8, 22).

2.0 Significance and relevance

Relevance and Significance: B-CLL cells constitutively secrete cytokines (IL-1, IL-6, and TNF-á) that are known to regulate sleep and fatigue. Lenalidomide has been shown to reduce the production of inflammatory cytokines by leukemic cells as well as normal leukocytes. By the conduct of this study we will obtain preliminary data on the role of lenalidomide on sleep and fatigue using validated assessment tools, objective measures(PSG, actigraphy) and laboratory correlates including the cytokines (IL-1 , TNF-á, IL-8, IL-10 and IL-6). We will use this preliminary data to conduct a larger randomized control trial for the effective treatment of sleep disturbances and fatigue.

3.0 Rationale

CLL most prevalent leukemia found in adults. CLL is common among the elderly and more than half of the patients are seventy years or older at the time of their diagnosis. Elderly patients with chronic lymphocytic leukemia (CLL) experience severe cancer related fatigue (CRF) (1). CRF is the most distressing symptom and has a severe psychosocial impact on their quality of life (QOL) and ability to receive treatment (1-7). Sleep disturbances is an important predictor for severe fatigue in patients with cancer (6). In prior studies, patients with B-CLL, the most self-reported severe symptoms were fatigue, sleep disturbance, drowsiness, distress, and shortness of breath. **Rationale**; Despite CRF's and sleep disturbances frequency, severity, and effects on the quality of life of these patients, there are limited treatment options available. There is an increased in inflammatory cytokines such as IL-1â, IL-6, IL-8, IL-10 and TNF-á are known to cause fatigue/sleep disturbances in cancer patients (6). Inflammatory cytokines are increased in patients with CLL, but there have been no studies correlating change of sleep disturbances and fatigue and changes in inflammatory cytokines in these patients. Recently, lenalidomide has been used for the treatment of various hematological malignancies. Lenalidomide is known to reduce inflammatory cytokines (IL-1 â, TNF-á, IL-6, IL-12, COX-2 and PGE2)(8). Preliminary studies in a noncancer disease Reflex sympathetic dystrophy showed that Lenalidomide improves sleep. Therefore, the effect of treatment with lenalidomide on sleep disturbances, fatigue and other associated symptoms in patients with CLL warrants investigation using validated assessment tools, clinical objective measures and laboratory correlates such as inflammatory cytokines. By the conduct of this pilot study in elderly patients with CLL undergoing front-line treatment with lenalidomide, we will obtain important preliminary data for a larger trial. We plan to accomplish this goal by using validated assessment tools, objective measures such as polysomnography, actigraphy and

laboratory correlates on the effect of treatment of lenalidomide on sleep disturbances and fatigue and IL-1, IL-6, IL-8 and TNF-á, IL-10 and MIP-1 to understand the pathobiology of these symptoms.

4.0 Hypothesis

We **hypothesize** that Lenalidomide improves total sleep time and fatigue in patients with CLL.

5.0 Specific aims

A. To determine the change in total sleep time as measured by polysomnography(PSG) in CLL patients with fatigue of ≥ 4(on a 0-10 scale) on the MD Anderson symptom inventory (MDASI) before and after the 1st cycle of treatment (day 57 +/- 3 days) with lenalidomide,

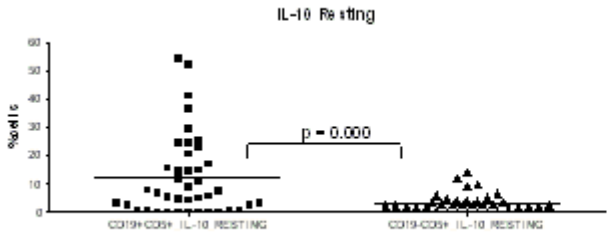
B.1. To summarize variables associated with sleep architecture as measured by PSG before and after the 1st cycle of treatment (57 days +/- 3 days) with lenalidomide, in this subset of population,

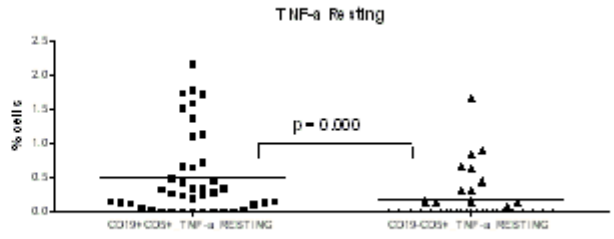
B.2. To summarize the variables associated with PSQI, Epworth sleep scale, actigraphy in relation to sleep and FACIT-F in relation to fatigue before and after treatment (57 days +/- 3 days) with lenalidomide.

B.3. To determine the relationship between changes in inflammatory cytokines levels and the frequency and intensity of fatigue and sleep disturbances in these patients as measured by the MDASI before and after the 1st cycle of treatment (57 days +/- 3 days) with lenalidomide.

6.0 Preliminary results

1. **Cytokine production by B cells of a patient with CLL**
Our preliminary data indicated that a statistically significant higher percentage of resting CD5+CD19+ leukemic B cells from B-CLL patients produced IL-10 (4a) and TNF- (4b), cytokines known to enhance the survival of B-CLL cells. These results suggest that upregulated levels of inflammatory cytokines might facilitate the development of a high tumor and symptom burden in B-CLL patients.





2. Elevated plasma level of inflammatory cytokines in untreated patients with CLL.

Compared with healthy controls (N=7), untreated B-CLL patients (N=17) had significantly higher plasma levels of IL-1 receptor antagonist, IL-2, soluble IL-2 receptor, IFN-ã, IFN--á, IL-4, IL-6, IL-8, IL-10,IL-12,TNF-,andTNF-receptor1.

7.0 Patient Eligibility

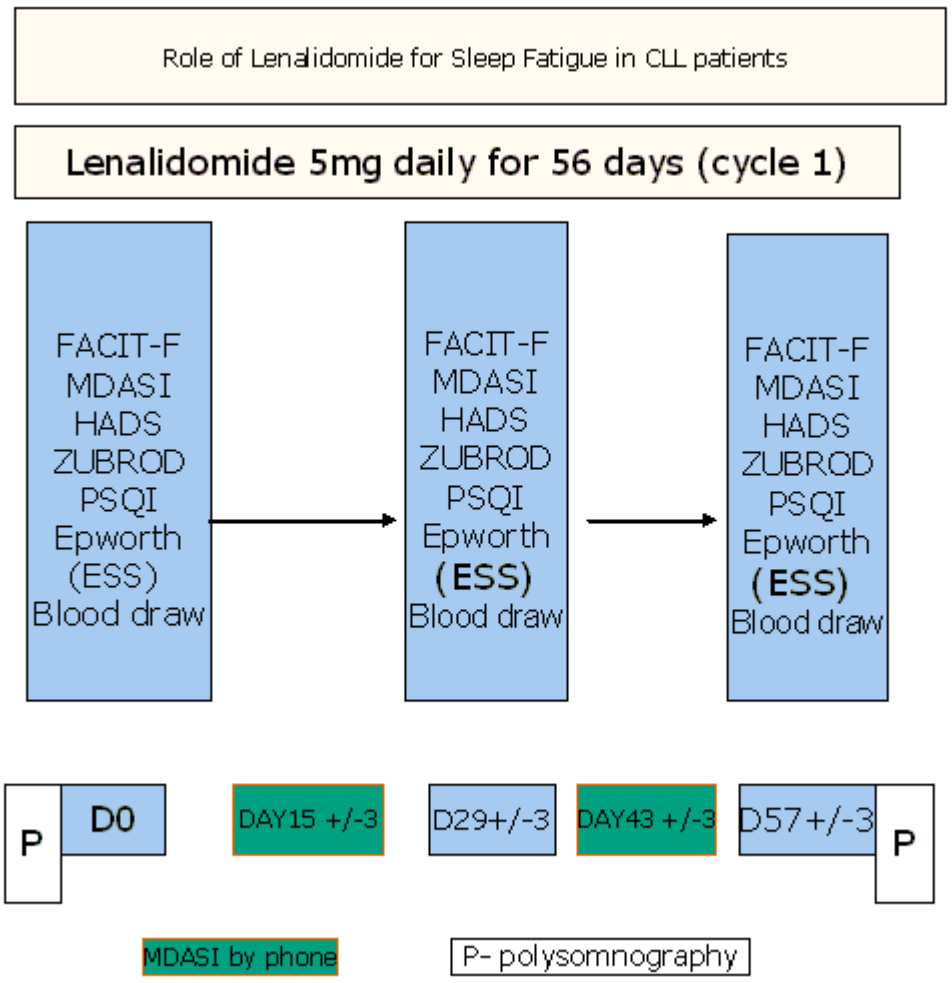
Inclusion criteria:

1.Patients to be 65 yrs or older.
2.Describe fatigue as being present every day for most of day for a minimum of 2 weeks and rate fatigue greater than or equal to 4 on a 0-10 scale, in which 0= no fatigue and 10=worst possible fatigue. .
3. Have diagnoses of CLL and enrolled in a clinical trial of lenolidomide to treat CLL[A phase II study of lenalidomide as initial treatment of patients with chronic lymphocytic leukemia age 65 or older - 2006-0715, A Study of Lenalidomide in Patients with Chronic Lymphocytic Leukemia and Residual Disease after Chemotherapy -2007-0213]
4. Patients will be eligible to participate in this study if they rate sleep disturbance greater than or equal to 4 on a 0-10 scale, in which 0= disturbed sleep is not present and 10 = disturbed sleep as bad as you can imagine.
5. Have a MDAS of 13 or less.
6. Able to understand the description of the study and give written informed consent.

Exclusion Criteria:

1. Patients who are unable to complete the assessment measures or refuse to participate.
2. Patients with known history of brain metastasis.
3. Patients with known history of sleep apnea.

8.0 Treatment Plan



Twelve eligible patients with CLL will be recruited from the Leukemia Clinic at MDACC. Patients complete questionnaires - MD Anderson symptom inventory(MDASI) for cancer related symptoms and screening for eligibility, Pittsburg Sleep Quality Index (PSQI), Epworth sedation scale, for assessment of sleep, FACIT-F to evaluate fatigue and quality of life and performance status is measured by Zubrod performance status and anxiety depression - Hospital anxiety depression scale(HADS). The laboratory correlates will include baseline hemoglobin level, electrolytes, serum IL-1, IL-6, IL-8 and TNF-á, IL-10 and MIP-1. This assessment will be performed a day before the initiation of therapy. Repeat assessments will be done on day 29 (+/- 3 days), and Day 57 (+/- 3 days), and again prior to the initiation of the next treatment phase. The day 15 (+/- 3 days) and day 43 (+/- 3 days) symptoms assessments will be performed via telephone. During the treatment period patient will wear an actigraph on the wrist to monitor physical activity. The actigraph will be used to record and evaluate sleep quantity and quality, daytime activity levels. Patient will maintain a sleep and fatigue dairy during the course of the treatment from prior to Day 1 to prior to the next treatment phase (at least 2 days). Patient will undergo polysomnography (PSG) to evaluate sleep pattern prior to Day 1 (after initial oncological visit) and prior to the next treatment phase (Day 57 (+/- 3 days)), at least 2 days prior to the initiation of treatment).

9.0 Outcome Measures

a) **MD Anderson symptom inventory (MDASI**) (Appendix D): This tool was designed to assist in the assessment of 13 symptoms common in cancer patients: pain, fatigue, nausea, depression, anxiety, drowsiness, shortness of breath, appetite, and sleep during the previous 24 hours. The severity at the time of assessment of each symptom is rated from 0 to 10 on a numerical scale, 0 meaning that symptom is absent and 10 meaning that it is of the worst possible severity. The instruments and techniques are both valid and reliable in the assessment of the intensity of symptoms in cancer populations (23).

b) **Pittsburg Sleep Quality Index (PSQI)**(Appendix G)**:** The PSQI is an effective instrument for assessing the quality and patterns of sleep in older adults. It differentiates between “poor” and “good” sleep by measuring seven areas during the month prior to assessment: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. The client self-rates each of these seven areas of sleep. The PSQI has internal consistency and a reliability coefficient (Cronbach’s alpha) of 0.83 for its seven components. This assessment would be performed on prior to Day1, Day 29 (+/- 3 days), and prior to the 2nd cycle (at least 2 days prior to the initiation of treatment)(24).

c) **The Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F)**(Appendix F)**:** The FACIT-F fatigue subscale has been used primarily in cancer patients to measure fatigue. The subscale consists of 13 items. Patients rate the intensity of fatigue and its related symptoms on a scale of 0-4, from 0 “not at all” to 4 “very much”. Test-retest reliability coefficients for the fatigue subscale have ranged from 0.84-0.90. This scale has demonstrated strong internal consistency (alpha=0.93-0.95). This assessment would be performed on prior to Day 1, Day 29 (+/- 3 days), and prior to the 2nd cycle (at least 2 days prior to the initiation of treatment)(25).

d) **Hospital Anxiety and Depression Scale (HADS)** (Appendix J): This 14 item questionnaire to assess patients’ anxiety and depression has been validated in a number of clinical situations and has been widely used in medically ill patients

e) **The Epworth sleep scale(ESS)**(Appendix H) is an 8-item questionnaire designed to asses general level of daytime sleepiness, and scores on this instrument range form 0-24, with higher scores indicating greater sleepiness.

Reliability has been tested for both scales and found to be good. A previous study determined within-subject reliability among 91 subjects who completed the PSQI on 2 occasions on average of 28 days apart. The Pearson correlation coefficient for the global score was 0.85(33). The Pearson coefficient in a trail involving 87 medical student over 5 months was 0.82.6 A study of the stability of both scores in 600 patients over one year was 0.68 and 0.76 for the PSQI and ESS respectively(34-36). The wide use of these validated instruments form the rational for using these scores to measure sleep quality and daytime sleepiness in our subjects(26-29).

f)**Sleep Diaries**: Sleep Diaries assess the following daily information: time of going to bed, final awakening, and arising from bed, sleep onset latency (SOL), numbers of awakenings (NWAK), wake after sleep onset (WASO), total sleep time (TSTS), sleep efficiency (SE), timing and duration of naps , and in the Pittsburgh Sleep Diary(PSD), sleep quality (30). Despite being subject reported they are widely used in research and in fact recommended I and considered essential in study of insomnia and other sleep disorders. The PSD has been used in numerous other sites to studies to evaluated sleep parameters(31).

g) **Actigraphy:** the measurement of physical movement using motion sensors reliably detects movements. As discussed in a major review and practice parameters (32), actigraphy provides an objective estimate of sleep and the 24-hour sleep wake rhythm and can detect circadian disturbances. Actigraphy can also be used to identify patients with sleep disorders who are overly active near bedtime or generally inactive throughout the day (33). Actigraphy will be measured from Day 0 to Day 57 (+/- 3 days).

h) **Polysomnography** (PSG) is considered the “gold standard” for the objective measurement of sleep parameters. Recoding details are as follows. PSG is recommended or essential in the study of sleep disorders such as insomnia in determining Total sleep time, SOL, NWAK, WASO, SE, Apnea Hypopnea Index, PLMAI (Periodic Limb Movement Arousal Index), arousals and stages of sleep (sleep architecture)(30). PSG will be performed at the UT MDACC Sleep Center (directed by Dr. Dave Balachandran, co-Investigator) by a registered polysomnographic technologist. A sleep variable will be obtained using 12-channel polysomnography (Nihon Kohden, Foothills Ranch, CA). The twelve channels of data will include: central and occipital electroencephalogram, bilateral electrooculogram, submental electromyogram, thoracic and abdominal respiratory effort, airflow, electrocardiogram, tibialis electromyogram, and oximetry. Sleep record will be scored by registered polysomnographic technologists according to the standard criteria of Rechtschaffen and Kales. Records will be scored for total sleep time, number of minutes of wake after sleep onset (WASO), number of awakenings, sleep latency, sleep efficiency, and the percentages of stages 1,2,3,4, and REM sleep, as well as cortical arousals (defined as sudden increases in electroencephalogram frequency of at least 3 second duration, following at least 10 seconds of continuous sleep, with or without accompanying muscle activity). Study participation will involve 12 hours including arrival at the Sleep Center at approximately 8pm, completion of questionnaires, instrumentation with sensors, and completion of post sleep questionnaires. This assessment would be performed on prior to Day 1 and prior to the 2nd cycle (Day 57 (+/- 3 days)), at least 2 days prior to the initiation of treatment).

Laboratory evaluation: serum cytokines (IL-1, TNF-, IL-8, IL-10 and IL-6) at baseline before treatment, day 29 (+/- 3 days) and day 57 (+/- 3 days).

Cytokine Measures: The serum samples will be stored frozen for subsequent batch analysis to construct a cytokine profile. The cytokine profile will be correlated with the degree of symptoms and for the responsiveness or failure to respond to lenalidomide therapy. Pro-inflammatory sleep inducing cytokines (IL-1, IL-6, IL-8 and TNF-á, IL-10 and MIP-1), anti-inflammatory anti-sleep inducing cytokine IL-10 will be measured in the serum of patients using the Multiplex Luminex Assay platform and commercially available cytokine-coated beads (Biosource Inc.). The Multiplex Bead Immunoassay will be used to measure serum/plasma levels of these cytokines and the assay sensitivity for these cytokines is 3-6 pg/mL. The Multiplex Bead immunoassay represents the development of a Multiplex Assay is designed to work in conjunction with the Luminex 100 analyzer (Luminex Corp., Austin, TX), associated software and fluorescently encoded microspheres. In this assay, each microsphere is labeled with a distinguishable fluorophore that allows it to be assigned or gated to a particular region by the scanner. Antibodies, specific for the cytokine or protein of interest (purchased from Biosource International, Camarillo, CA) are covalently linked to individually beads of a different fluorescent marker. When the beads are reacted with sera or plasma containing cytokines, the cytokines bind to the bead coated with the complementary antibody, and its unique fluorescent signature can detect cytokine-bead complex by the Luminex 100 analyzer. These assays have been performedinDr.Reuben’slaboratory.

10.0 Statistics

The primary objective is to explore a change in total sleep time using Polysomnography (PSG) in CLL patients with fatigue of greator or equal to 4 (in a 0-10 scale) on the MD Anderson symptom inventory (MDASI) before and after the 1st cycle of treatment (57days) with a Lenalidomide. We will use a paired t test, a Wilcoxon rank sum test, or a sign test (depending on the distribution of the data) to determine changes in total sleep time before and after treatment (day 57). Prior studies have indicated a clinically significant change in the total sleep time estimated by PSG to be 20 min, using a pilot open labeled design we anticipate obtaining a similar outcome by accruing 12 patients (34). Due to the challenge of accrual, expense and time constraints, a relatively small sample size has been selected. Assuming we will enroll 12 evaluable patients, we will be able to declare as significant differences between pre and post that are 0.89 standard deviations or greater with 80% power and a two-sided significance level of 0.05. We will summarize variables associated with sleep (PSG, Actigraphy, PSQI, ESS), fatigue (FACIT- F, HADS, actigraphy) and serum cytokines (IL-1, IL-6, IL-8 and TNF-á, IL-10 and MIP-1). In addition we will correlate these variables with changes in sleep time, using Pearson or Spearman correlation coefficients, depending on the distribution of the data. In addition this study will obtain preliminary data to determine the effect size for a future larger randomized controlledtrial.

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