MD Anderson IND Sponsor Cover Sheet

Protocol ID	2012-0120
Protocol Title	Multimodal Therapy For The Treatment Of Sleep Disturbance In Patients With Cancer
Protocol Phase	II
Protocol Version	15
Version Date	07/07/2020
Protocol PI	Sriram Yennu, MD, MS
Department	Palliative Care and Rehabilitation Medicine
IND Sponsor	MD Anderson Cancer Center
IND #	115546

Structured Abstract

Primary objective:
Aim 1. To obtain preliminary estimates of the effects of CBT and various treatments[light therapy, melatonin, Methylphenidate] and combinations of treatments in MMT in reducing sleep disturbance in patients with cancer, as measured by change in PSQI scores taken at baseline and on Day 15.

Secondary objectives:
Aim 2. To explore the effect of MMT on Insomnia Severity Index, cancer related symptoms [fatigue (FACIT-F subscale, ESAS), anxiety ,depression anxiety (Hospital Anxiety Depression Scale [HADS], ESAS), quality of life(FACT-G, ESAS), and physical activity/sleep efficacy (Actigraphy), before and after treatment with various SD treatment combinations of MMT;
Aim 3. To determine the safety of MMT (type, frequency, and severity of the adverse events).

The primary outcome variable for this study is the change in PSQI score.

Sleep Disturbance (SD) occurs in 24%–95% of patients with cancer [1-3]. In recent study at supportive care center at UT MDACC, 75% (330/440) were diagnosed to have moderate to severe sleep disturbance (4). Patients who experience SD can also experience significant distress due to decline in cognitive function, an inability to engage in work or recreational activities, loss of hedonic capacity, lower quality of life, and adverse alterations to immune and neuroendocrine functions [2,5-7]. Even so, SD is frequently underdiagnosed and undertreated in clinical oncology practice [2,3, 5]. Although SD is common and distressing in patients with advanced cancer, there are limited treatment options in patients with advanced cancer. One reason for the lack of effective treatments is that few controlled studies targeting SD; hence, further studies are needed [2,9].

The proposed study would determine the effect of various combinations of light therapy, melatonin, and methylphenidate with cognitive behavioral therapy (that is, multimodal therapy, or MMT) for the treatment for SD; if effective, these low-cost, low-risk; easily accessible interventions would potentially benefit many other cancer patients. The factorial design utilized in this study will test not only the preliminary outcomes and adherence of each individual treatment (light therapy [2,10-14], melatonin[15-18], methylphenidate (MP) [19-22] and cognitive behavioral therapy (CBT) [3,23-27], but also their combinations which we hypothesize will produce a larger reduction in SD. Thus, data collected from this novel randomized factorial design will enable us to assess the three treatments used in this study without the need for a second, larger study, but if one or more treatment combinations do appear effective, a larger study will be designed using estimates of intersubject variability and treatment efficacies estimated from the present design.

Innovation. We consider this study innovative because we will obtain important data about preliminary outcomes and patients' adherence to MMT in a randomized controlled trial including all the proposed interventions in patients with SD. The factorial design is highly innovative for assessing treatments for SD because it allows us to study the effects three safe, readily available and low-cost interventions and their combinations simultaneously with CBT in one clinical study in comparison to other traditional designs which would require multiple individual clinical trials requiring a longer time to complete and be very costly, rendering them to be a less feasible option. This study is novel because not only will the data collected from this randomized factorial design be used to assess the main effects CBT and the three treatments for SD, but also the factorial design will allow us to assess the synergies between the treatments. This study is also novel because we will use this innovative design performed in a very controlled setting in a well defined population.

Factorial designs are the standard experimental design used when it is possible to give treatment combinations [28,29]. This is the advantage of factorial designs and why they are used so predominantly in industrial experiments. As Fisher [28] showed, experimental designs that test only two treatment groups at a time are highly inefficient. A factorial design allows the effect of several factors and interactions between them to be determined by using the same number of patients that would be necessary to estimate a single treatment. The only reason that factorial designs are not commonly used in oncology trials is that toxicity due to combined treatments is generally an overriding concern in administering cytotoxic agents to cancer patients. Based on prior clinical trials, the study interventions (cognitive behavioral therapy [3,23-27], light therapy,melatonin and methylphenidate [2,10-22]) are not expected to result in toxic effects in patients, either alone or in combination. Factorial design would be ideal to test multidimensional symptom interventions or their combinations necessary to treat the multifactorial nature of SD. And lastly assessment of SD requires the use of continuous scales unlike physician reported outcomes for cancer trials, analyses of which require sophisticated analyses.

In this study, we will assess 3 treatments (light therapy, melatonin, and methylphenidate) and their placebos treatments with CBT in 8 replications of a complete factorial design. A total of 32 patients will receive each primary treatment and 32 will not. Within each group of 32, the allocation of the other treatment combinations will be balanced so that the additive effects of the other treatments cancel out; this means that we will be able to make comparisons between each of the 3 main treatments with the same level of accuracy as if we had performed 3 trials, each with 64 patients. In other words, the variance of the estimate of the main treatment effects is the same as if the trial had been performed with 64 patients, 32 receiving treatment and 32 receiving placebo. For the three second-order interactions, comparisons will have the same error variance that would have been estimated with 16 patients assigned to the two-drug combination and 48 to placebo. The variance of the estimate of the effect of the 3-drug combination will be similar to the variance that would be estimated if 8 of 64 patients were receiving the three drug combination and 56 were receiving the placebo. The objective of the proposed project is to explore the effects of MMT on SD and safety in patients with cancer. We hypothesize that MMT is capable of reducing SD as measured by the PSQI in these cancer patients (Fig. 1). To achieve this objective, we plan to use a randomized factorial design.

I. BACKGROUND

SD is common and under diagnosed in patients with advanced cancer. SD is common in patients with advanced cancer, and its impact is not always recognized [1-3,30]. The prevalence of SD in patients with advanced cancer reported in the literature is variable with a range between 24% and 95% [1-3,30]. This wide range reflects the variability of diagnostic criteria, tools and methodologies used. In recent study at supportive care center at UT MD Anderson Cancer Center 75% (330/440) were diagnosed to have moderate to severe sleep disturbance(4).

Patients who experience SD can experience significant distress due to decline in cognitive function, an inability to engage in work or recreational activities, loss of hedonic capacity and adverse changes in the immune and neuroendocrine functions [2,3,5-7. SD is also associated with worse quality of life and increase in the intensity of symptoms such as pain, depression and anxiety [2,3]. It has been suggested that sleep-wake and circadian rhythm disturbances are associated with increased mortality in patients with metastatic disease [31]. Despite its relevance, SD is frequently under diagnosed and undertreated in clinical oncology practice [2,25].

A. Pathophysiologic mechanisms of SD in patients with advanced cancer

Cancer patients are at an increased risk for altered sleep pattern and disruption of the normal behaviors and physiology that lead to a restful sleep [2,3,25**].** Multiple physiologic mechanisms are altered in patients with advanced cancer. Patients with cancer have abnormalities in the circadian regulatory process, with alterations in the production of cortisol, melatonin and cytokines [2]. Recent research has recognized the role of the immune system and inflammatory mediators as an organic component in the disruption of the sleep cycle in patients with sleep disturbance [32-36]. Patients have changes in their daily routine, with decreased daytime activity and increased time in bed [37]. They also experience increased physical symptoms such as pain or dyspnea, which are associated with sleep disruption affecting both sleep onset and maintenance [25,30,31]. Finally, psychosocial stressors are frequent in cancer patients and can also contribute to sleep disturbances in this population. Hospice patients themselves recognize that physical symptoms, worries about the disease, the family and the future are the main causes of sleep disturbance [30]. All these mechanisms involved in sleep disturbance influence each other establishing an intricate network of interactions between them. This complex interaction makes the treatment of this distressing symptom very challenging.

a. **Immunity - Inflammation:** Some cytokines regulate sleep under physiologic conditions, in the absence of infection or immune challenge [31,36]. Research during the last decade has described a close relationship between inflammation and sleep patterns, and this relationship seems to be bidirectional: impaired sleep can modify cytokine levels and inflammation itself can modulate wake-sleep pattern. Given the increased level of cytokines in patients with cancer it is possible that inflammation could have a role in the increased prevalence of SD in these patients.

   Sleep deprivation in normal subjects alters the immune system with decreased activity of natural killers (NK) cells and increased T-helper cells [25,31,34-36]. Healthy people exposed to modest sleep restriction are not only sleepier during the day and have impairment in psychomotor

performance tests, they also have increased secretions of cytokines [35,36]. Specifically, IL-1, TNFα and IL-6 are cytokines that have been identified as involved in altered sleep patterns. Chronic insomnia is also associated with cytokine changes. These patients have a shift in the peak levels of IL-6 and TNFα from nighttime to daytime, that could explain the fatigue and detrimental performance associated with insomnia [31,32]. It has also been suggested that chronic sleep impairment, as occur in patients with advanced cancer, could contribute to inflammation through desynchronization of circadian rhythms (e.g decreased rhythmic variation of cortisol) [31],

On the opposite direction, inflammation may contribute to the development of behavioral alterations, such as SD, both in healthy and sick individuals. Studies in animals have shown that strong host defense responses are associated with suppression of REM sleep. Likewise, intense immune responses during infection are associated with increased non REM sleep and probably survival [34]. It is thought that immune cytokines induce behavioral changes through modulation of brain neurotransmitters, hypothalamic-pituitary-adrenal axis and regional brain activity [31]. Even though it has not been specifically studied, it is possible that inflammation could be an important trigger/mediator of altered sleep patterns in patients with advanced cancer.

b. **Behavioral factors:** Conditions that maintain insomnia are maladaptive sleep habits and dysfunctional cognitions that patients develop in reaction to SD. These two factors increase arousal and performance anxiety, which are opposite to the relaxation state required to initiate sleep. These maladaptive behaviors are particularly frequent in cancer patients. They are encouraged to rest and sleep as much as they can to recover from cancer treatments, impairing normal sleep habits. In this same direction, patients spend long time in bed doing wakening promoting activities, such as watching TV or listening to music, which in turn weaken the normal association between stimuli that promote sleep (e.g. like going to bed at bedtime, with sleeping itself) [37].

   Increased time in bed and lack of exercise: Exercise improves sleep by direct brain effects and by modulating the inflammatory cytokines such as TNF-α, IL-6 levels [31]. Likewise CBT potentially reduce CBT by its action on IL-6, TNF-α [85, 90-93],

c. **Physical symptoms:** Pain is a frequent symptom in patients with cancer [37]. Patients with severe pain often report more sleep disturbances [37, 38]. Pain affects both initiation and maintenance of sleep and one possible mechanism is increased arousal. It is thought/ has been demonstrated that patients with pain have increased adrenergic response, associated with activation of the HPA axis, which stimulates arousal and decreases sleep.

   Fatigue is one of the most important complains in patients with insomnia. Cancer patients often experience fatigue secondary to the cancer itself and to cancer treatment.

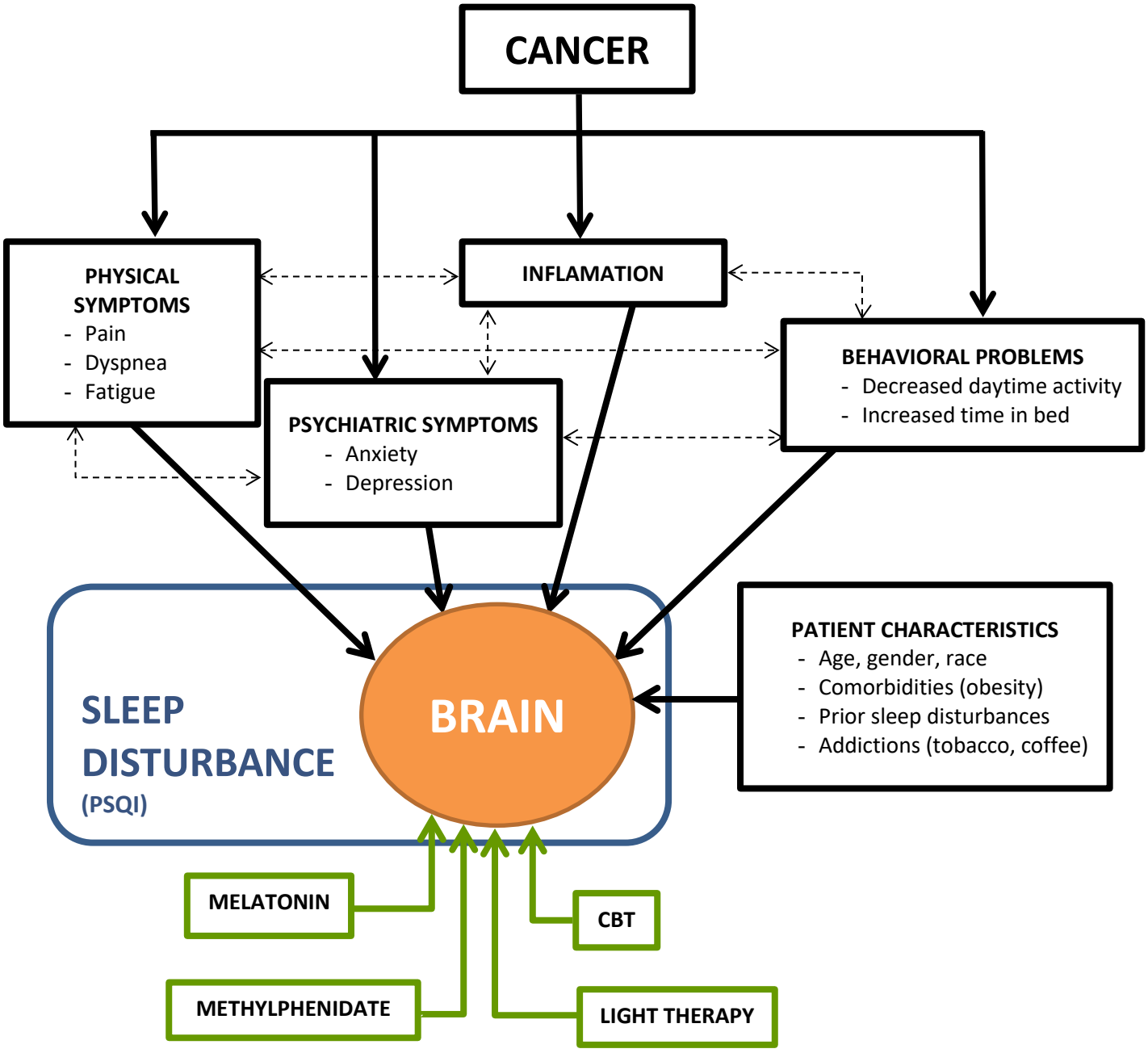
   Dyspnea is associated with frequent interruptions sleep [2,25,30,37]. Fatigue is associated to increased cytokines and changes in behavioral factors [25,31].

d. **Psychosocial stressors:** Anxiety and Depression are associated to increased arousal. Sleep disturbance often coexists with psychiatric diseases such as depression and anxiety. These diseases can be both cause and consequence of insomnia [25].

e. **Aging:** patients require less sleep as patient's age (25).

f. **Other mechanisms:** sleep apnea, restless leg syndrome (25)

Figure 1: Conceptual model.



B. Interventions for treatment of sleep disturbances in patients with advanced cancer

Current treatments for SD in cancer patients are not effective. There are multiple interventions available to treat SD in patients with advanced cancer, but current treatments are not always effective. A reasonable first approach is to address underlying physical and psychological factors involved in sleep disturbances, such as pain, dyspnea or anxiety. At the same time, both non-pharmacological and pharmacological interventions can be implemented that directly treats this symptom. Both types of interventions have been studied. Among the non-pharmacologic interventions, cognitive based therapy and light therapy for SD in patients with cancer have been described in the literature with mixed results. Among the pharmacologic interventions, melatonin and methylphenidate have shown some improvement. However, the results have not been consistent, hence need for further studies.

Type	Intervention	Effect in General Population	Effect in Cancer Patients
Non-pharmacologic	CBT	Level 1 evidence for short-term effects. Reduces sleep onset latency and wake after sleep onset [39]. Includes: Stimulus control, progressive muscle relaxation, paradoxical intention, biofeedback and sleep restriction [40]. Multicomponent BT is effective. CBT is effective [41].	Yes, likely to be effective [2,42].
	Exercise	Recommended by American Sleep Disorders Association, but there are still conflicting results [43].	Positive trend to improve sleep [42].
	Light Therapy	Yes, especially in patients with circadian rhythm disorders [44].	Yes, likely to be beneficial {12, 13}
Pharmacologic	Benzodiazepines	Yes, reduce self-reported sleep onset latency time & number of awakenings and improve self-reported sleep duration, total sleep time and sleep quality. Reported increased daytime sleepiness, dizziness and lightheadedness [9]. Long term use can result in disrupted sleep pattern with fragmented sleep and dependence on the medication [20]. Also concern about drug interactions.	Can be deleterious to the palliative care patients [37].
	Non-benzodiazepine hypnotics	Yes, reduce self-reported sleep onset latency time & number of awakenings and improve self-reported sleep duration, total sleep time and sleep quality [9]. Same precautions as with benzodiazepines [20]. (More expensive than benzodiazepines).	Yes, likely to be beneficial[25]
	Methylphenidate	In healthy individuals who are experiencing sleep loss, methylphenidate improves psychomotor performance [38].	Yes, likely to be effective[22]
	Melatonin	Yes, but minimal clinical benefits, with reduced sleep latency and increased sleep duration and sleep efficiency [39]. Demonstrated effect in patients with disruption of the circadian rhythm of melatonin secretion.	Not demonstrated in patients with cancer. It could have a role as immunogenic agent [15].

	Antidepressants	No strong evidence to favor its use in general population [20].	Specific antidepressants recommended in patients with insomnia and depression or neuropathic pain [25].

Non - pharmacologic interventions:

CBT: cognitive and behavioral interventions are defined as treatments that aim to improve sleep by changing poor sleep habits and challenging negative thoughts, attitudes and beliefs about sleep [39-41]. The interventions include stimulus control, sleep restriction, sleep hygiene education, relaxation and cognitive therapy. The use of simultaneous interventions has proven more effective than interventions alone [37]. These interventions are clearly effective in patients with primary insomnia. There are some studies in patients with advanced cancer in which different multimodal interventions, including stimulus control, relaxation training, mindfulness practices, exercise and reducing levels of arousal and sleep hygiene, improved sleep and fatigue and enhanced ability to perform activities [42,48. However, few studies had a randomized control design or more than 100 patients. Hence, the evidence is not strong for the effectiveness of these interventions specifically in cancer patients [2].

Light therapy: Evidence not clear[10-13].
Seasonal Affective Disorders and other disorders that involved chronobiological malalignments like circadian sleep phase disorder, jet lag and shift work syndrome showed similar benefits with light therapy. Using the Litebook®, Ancoli-Israel et al. found that 1350 Lux of LED light for 30 minutes every morning improved sleep in patients with breast cancer undergoing chemotherapy compared to dim red light (13,Ancoli-Israel et al., personal communication). Light therapy also has some effect in non-seasonal depression (11,Tunainen Cochrane Database; Golden RN Am J Psychiatry). Exposure to bright light has been shown to improve sleep-wake quality.(12,Termin J Bio Rh Bright light therapy also has been effective in sleep disturbances among nursing home patients with dementia. 50 Light, at intensity between 6,000 to 8,000 lux, was given for 2h/day during morning hours for 2 weeks, the only side effects reported were minor eye-irritation in the first 4-5 minutes of bight-light exposure, that gradually disappear after some days of treatment.

Side effects are usually mild. Terman et al. reported mild side effects of bright light therapy in the treatment of depression in 38 patients, receiving a dose of 10,000 lux daily for 30 minutes in the morning or evening[12]. These include jumpiness/jitteriness (9%), headache (8%) and nausea/vomiting (16%), and eye irritation (12%).

Pharmacologic interventions
Methylphenidate: evidence in patients with advanced cancer (21,22).
Patient with advanced cancer have significant cancer related fatigue (CRF). Prior studies have found that SD and CRF are correlated. Prior studies of Methylphenidate for the treatment of sleep disturbance showed that sleep disturbance after treatment with methylphenidate showed significant improvement compared to baseline (see Table 1).

Table 1. Sleep Quality between Day 8 and Baseline in Patients taking Methylphenidate[22]

	Methylphenidate (n = 52)				
	Baseline		Day 8		
Sleep Pattern	Mean	SD	Mean	SD	*P*
Difficulty of falling asleep (0-10)*	3.4	3.2	2.4	2.7	.03
Rested in the morning (0 to 10)*	6.3	3.4	4.5	3.2	< .001
Problem with sleep (0 to 10)*	4.7	3.3	3.9	3.3	.10
Importance of lacking sleep (1 to 7)†	4.4	2.1	3.8	2.0	.03

Abbreviation: SD, standard deviation.
*0 = best, 10 = worst.
†1 = not important; 7 = great importance.

- **Melatonin:** Evidence in patients with delayed sleep phase disorder onset no evidence in patients with advanced cancer (15-18)
- **In patients with primary sleep disorders:** Melatonin decreased sleep onset latency in people with a primary sleep disorder (WMD: -10.7 min; 95-percent CI: -17.6 min, -3.7 min). SOL was decreased greatly in people with delayed sleep phase syndrome (WMD: -38.8 min; 95-percent CI: -50.3 min, -27.3 min). The magnitude of this effect appears to be clinically significant. SOL was decreased marginally in patients with insomnia (WMD: -4.3min; 95-percent CI: - 8.4 min, -0.1 min.). The magnitude of this effect appears to be clinically insignificant. SOL was reduced more in children (less than age 17 years) (WMD: -17.0 min, 95-percent CI: -33.5 min, -0.5 min) than in adults (age 18-65 years) (WMD: -11.2; 95-percent CI: -27.7 min, 5.4 min) or elderly patients (greater than age 65 years) (WMD: -7.8 min; 95-percent CI: -17.4 min, 1.7 min). The effects of melatonin did not vary with dose or duration of treatment. If the analysis is approached using the Fixed Effects Model, melatonin does not have any effect on sleep onset latency in people with primary insomnia.
- Melatonin did not have an effect on sleep efficiency in people with primary sleep disorders; the effects of melatonin did not vary by age, type of primary sleep disorder, dose, or duration of treatment.
- Melatonin did not have an effect on sleep quality, wakefulness after sleep onset (WASO), total sleep time, or percent time spent in REM sleep.
- Generally, these studies were of moderate-to-high quality.

In patients with secondary sleep disorders:

Melatonin did not have an effect on sleep onset latency in people with a secondary sleep disorder; the effects of melatonin did not differ between children and adults; the effect of melatonin did not vary with dose or duration of treatment.

- Melatonin increased sleep efficiency in people with a secondary sleep disorder (WMD: 1.9 percent; 95-percent CI: 0.5 percent, 3.3 percent); the effect of melatonin did not vary by age, dose or duration of treatment. The magnitude of this effect appears to be clinically insignificant.

- Melatonin did not have an effect on WASO or percent time spent in REM sleep in people with a secondary sleep disorder, but increased total sleep time in this population
- Generally, these studies were of moderate-to-high quality.

Most studies use fast-release melatonin, but sustained-release preparations are commercially available. The doses used in most studies range from 0.5 to 20 mg [15].

Side effects

In general, melatonin seems to be well-tolerated, and few serious side effects have been reported to date. However, there is a lack of long-term studies, and little is known about the possible drug interactions.

Antidepressants can have a sleep induction profile, such as SSRIs and tricyclic antidepressants.

Hypnotics are the most common drug used to treat SD in patients with cancer.

Benzodiazepines: In general population, benzodiazepines are effective in short-term management of insomnia, decreasing sleep latency and mid night awakenings and increasing total sleep duration. There are no randomized controlled trials assessing the effectiveness of benzodiazepines on sleep initiation and sleep duration in cancer patients [37, 42]. Despite the evidence of this type of hypnotics in the short - term treatment of insomnia, little is known about long-term effect of benzodiazepines. A large number of side-effects are associated to the use of benzodiazepines, including drowsiness and dizziness, increased risk of falls and hip fractures, potentiation of hypoventilation in patients taking opioids and risk of tolerance and dependence [45].

Therefore, it is unlikely that an isolated intervention will be effective in treating this symptom.

C. Need for a Multimodal Therapy:

It is possible, that given the multiple factors that influence sleep, the effect of an isolated intervention might not be as effective as an intervention in which multiple factors are simultaneously addressed and treated. This idea is supported by the fact that several pathophysiologic mechanisms have been identified as mechanisms associated with the presence of sleep disturbances, and that each of the interventions to improve SD targets partially the mechanisms involved. We believe that a multimodal intervention to treat SD in patients with cancer, targeting all the known pathophysiologic mechanisms involved will have a synergistic effect, decrease the intensity and frequency of SD among these patients and as a consequence patient's quality of life.

D. Potential for interactions and synergism:

CBT, reduces SD by direct brain effects and by improving motivation and mood, which contribute to and exacerbate fatigue [2, 23-27]. MP will have a positive effect on SD via central mechanisms, that is, by blocking the reuptake of dopamine and norepinephrine, acting on the reticular activating system (arousal), and mood and by improvement of fatigue. We hypothesize that combinations of CBT with light therapy, melatonin and/or MP will confer additional benefits exceeding those conferred by each treatments alone (that is, that there will be a synergistic effect) [2, 10-22]. In patients with cancer and SD, melatonin improves fatigue direct brain effects related to fatigue, but also reduces fatigue by modulating the inflammatory cytokines such as TNFα, IL-6 levels [31]. Likewise CBT potentially reduce SD by its action on IL-6, TNFα [31,49,50], thus raising the possibility of synergism with melatonin. Prior findings also lead us to hypothesize that CBT has the potential for synergism with methylphenidate because of CBT's ability to reduce anxiety and improve mood by enhancing the neurotransmission of

noradrenaline, seratonin, 5-hydroxytryptamine, and dopamine [31]. In addition Light therapy, MP combined with CBT may have a synergistic effect in improvement of fatigue and thereby enhancing patients' SD [31,32-34,49-51].

E. Significance of the Study:

Despite CRF's prevalence, severity, and effects on cancer patients' QOL, few treatment options are available that can reduce SD [2,3]. One reason for this lack of effective treatments is that few controlled studies targeting SD have been conducted in patients with advanced cancer population. Hence, further studies are needed [2,37]. The significance of this study is that it will allow us to obtain important preliminary data about the effects (i.e., clinical benefits) of safe, easily accessible and low cost interventions such as CBT, Light Therapy, Melatonin and MP and their combinations in the treatment of SD. The data collected from this novel randomized factorial design will enable us to assess the treatments used in this study[rapidly and efficiently], and but if more than one treatment combinations do appear effective, a larger study will be designed using estimates of intersubject variability and treatment efficacies estimated from this design. Our ultimate goal is to develop a single, effective, low-cost, low-risk, easily accessible multimodal approach for the clinical management of SD that would potentially benefit many if not most cancer patients.

II. Research design:

A. Patient Recruitment:

Eligible subjects will be recruited from MD Anderson Cancer Center. Potential participants will be approached by the research personnel and provided information about the study. Handouts that explain the study description and how subjects may benefit from participation will be provided to the patients. (See Appendix S)

B. Feasibility

Feasibility is based on the prior successful accrual in similar symptom control trials by our group [21,22,52,53] and on the great interest in complementary and alternative medicine in this population (83%) [54].

C. Patient Eligibility

Patients: cancer patients currently on cancer therapy with a positive screening for SD (Screening PSQI score $\geq$ 5).

Inclusion criteria:

1. Patients who are 18 years or older, cancer patients currently on cancer therapy with a positive screening for SD (Screening PSQI score $\geq$ 5).
2. Patients should have a Zubrod </= 2.
3. Patients with no pain and with stable pain(defined as pain under control and on stable doses of opioids for 1 week) are eligible
4. Memorial delirium assessment scale </= 13.
5. Controlled pain and depression symptoms, if present (defined as no change in the Morphine equivalent dose of 30% or change in the dose of antidepressant medication in the past 2 weeks).
6. All patients who are receiving chemotherapy and/or radiation therapy are eligible for study if they have completed > 1 week of radiation therapy, and if they have been approved to go on study by their primary oncologist. The PI/designated research staff of this study will obtain and document approval from the primary oncologist and principal investigator of the clinical trial in case the patient is on another clinical trial as referenced in the patient's study documents.

7. Laboratory test results within these ranges: Serum creatinine </= 2.0 mg/dL, Total bilirubin </=1.5 mg/dL, and AST (SGOT) and ALT (SGPT) </=2 x ULN or </= 5 x ULN if hepatic metastases are present. ULN= upper limit of normal.
8. Patients on stable doses (defined as same dose for 2 weeks) of dexamethasone, mirtazapine, zolpidem, benzodiazepines, phenothiazines are allowed to participate in the study.

Exclusion criteria:

(1) Have a major contraindication to methylphenidate (MP) (e.g., allergy/hypersensitivity to study medications or their constituents), light therapy (e.g., currently receiving UVA/UVB therapy), cognitive behavioral therapy (e.g., schizophrenia), or conditions making adherence difficult as determined by the attending physician.
(2) Currently taking MP or have taken it within the previous 10 days.
(3) Patients with a diagnosis of polysomnographically confirmed obstructive sleep apnea or narcolepsy.
(4) Regularly used cognitive behavioral therapy in the last 6 weeks for sleep disturbance.
(5) Unable to complete the baseline assessment forms or to understand the recommendations for participation in the study.
(6) Currently with a diagnosis of major depression, manic depressive disorder, obsessive-compulsive disorder, or schizophrenia).
(7) Need monoamine oxidase inhibitors, tricyclic antidepressants, or clonidine.
(8) Have glaucoma.
(9) Symptomatic tachycardia and uncontrolled hypertension (determined to be clinically significant by the PI).
(10) Currently receiving anticonvulsants (phenobarbital, diphenylhydantoin, primidone), phenylbutazone, clonidine, and/or tricyclic drugs (imipramine, clomipramine, or desipramine).
(11) Unable to speak and understand English
(12) Persons with congenital blindness and self-reported acquired blindness (independent of the cause) with no light perception
(13) Patients with a history of retinal disease
(14) Patients with >2 hours of direct exposure to outdoor natural light per day by interview with the Study Coordinator.
(15) Patients with a diagnosis of obesity hypoventilation syndrome.
(16) Positive pregnancy test for women of childbearing potential, as defined by intact uterus and ovaries, and a history of menses within the last 12 months. Pregnancy test to be performed no greater than 14 days prior to consent in study. In cases of women with elevated b-HCG, these candidates will be eligible to participate so long as the level of b-HCG is not consistent with pregnancy. Women of childbearing potential need to be on or use contraception, or be abstinent during the study period. Their male partners must also use contraception (condom) or maintain abstinence. Birth controls specifications: Women who are able to become pregnant must use birth control during the study and for 30 days after.
(17) Women who are nursing.
(18) Patients who have taken Melatonin within the past two weeks.

D. Clinical Trial Design:

For this study, we will use a randomized factorial design. Sixty-four patients will be randomized equally among the 8 possible treatment combinations, 8 per arm. The randomized assignment of intervention versus placebo will be obtained via the Department of Biostatistics, Clinical Trial Conduct Website.

E. Treatment Plan:

Potential study subjects will be asked for verbal consent (Appendix Q) prior to completing the PSQI to determine eligibility.

Patients who are eligible (PSQI score $\geq$ 5) and interested in participating will be asked to give written consent and then randomized into 1 of the 8 arms of the study that include possible combinations of the 3 interventions or their corresponding placebo treatments. The length of treatment is 15 days with follow up at Day 29 (+/- 1 week). The research nurse/coordinator will conduct all baseline assessments and follow-up as shown Table 4. All patients will receive CBT. Patients will receive combination of light therapy, melatonin and methylphenidate or their placebos (Pharmacy Innovations) in addition to CBT as part of the multimodal therapy. The pharmacological treatment assigned to individual patients will be known to only the statistician and the investigational pharmacy. The research nurse will then provide instructions and prescriptions for the study medications (drug or placebo) and will make referrals to the counselor for CBT. The randomized assignment of intervention versus placebo will be obtained via the Department of Biostatistics, Clinical Trial Conduct Website. The research nurse/coordinator will then perform scheduled assessment as per Table 4. The research nurse/coordinator will check compliance during weekly telephone call or in person visit. Patients will be asked if they have been documenting the administration times on the patient diary/pill diary (See Appendix N).

Table 2. Treatment Arm Combinations (please see page 26 for description of arm combinations)

	Patient							
Intervention	1	2	3	4	5	6	7	8
Light Therapy	0	X	0	0	X	X	0	X
Melatonin	0	0	X	0	X	0	X	X
Methylphenidate	0	0	0	X	0	X	X	X
	Patient							
Intervention	9	10	11	12	11	14	15	16
Light Therapy	0	X	0	0	X	X	0	X
Melatonin	0	0	X	0	X	0	X	X
Methylphenidate	0	0	0	X	0	X	X	X
	Patient							
Intervention	17	18	19	20	21	22	23	24
Light Therapy	0	X	0	0	X	X	0	X
Melatonin	0	0	X	0	X	0	X	X
Methylphenidate	0	0	0	X	0	X	X	X
	Patient							
Intervention	25	26	27	28	29	30	31	32
Light Therapy	0	X	0	0	X	X	0	X
Melatonin	0	0	X	0	X	0	X	X
Methylphenidate	0	0	0	X	0	X	X	X

	Patient							
Intervention	33	34	35	36	37	38	39	40
Light Therapy	0	X	0	0	X	X	0	X
Melatonin	0	0	X	0	X	0	X	X
Methylphenidate	0	0	0	X	0	X	X	X
	Patient							
Intervention	41	42	43	44	45	46	47	48
Light Therapy	0	X	0	0	X	X	0	X
Melatonin	0	0	X	0	X	0	X	X
Methylphenidate	0	0	0	X	0	X	X	X
	Patient							
Intervention	49	50	51	52	53	54	55	56
Light Therapy	0	X	0	0	X	X	0	X
Melatonin	0	0	X	0	X	0	X	X
Methylphenidate	0	0	0	X	0	X	X	X
	Patient							
Intervention	57	58	59	60	61	62	63	64
Light Therapy	0	X	0	0	X	X	0	X
Melatonin	0	0	X	0	X	0	X	X
Methylphenidate	0	0	0	X	0	X	X	X

Placebo and control.
The matching placebo will consist of colored capsules of similar appearance and size, since methylphenidate has little or no odor that will need mimicking. The placebo will include the inactive excipient methylcellulose. A matching placebo will be used to eliminate the placebo effect as a result of intervention.

E.1 **Light treatment:** The active treatment is a Litebook device (The Litebook Company Ltd., Alberta, Canada). The device consists of 60 LEDs with spectral emission peak at approximately 464nm and fluorescent phosphors that provide a broader, secondary spectral peak near 564nm. Of the energy emitted over the range 400 to 700nm, about 48% is emitted over the range 420 to 508nm, and 37% is emitted over the range 512 to 616nm. Collectively the emitted light appears white. This device produces approximately 1350 lux at 20 inches.

The control red light device is also produced by Litebook (The Litebook Company Ltd), and is identical in appearance and dimensions to the bright light device, with the exception that it emits at wavelength 680nm (i.e. red light) and at an intensity of 50 lux. The manufacturer documentation of the shelf-life of the LiteBook device for both the placebo and active devices is 5 years.

While dim red light may not be the ideal control due to its different color, brightness and the fact that patients may find out that they are getting the control, we believe it is an appropriate choice for the following reasons:

1. Dim red light has been used as control intervention in multiple randomized trials studying the effect of bright light therapy.[51-53] In fact, a cancer fatigue study that is actively recruiting patients is using dim red light as control

(http://clinicaltrials.gov/ct2/show/NCT00478257?term=litebook&rank=1)

2. In our supportive care outpatient clinic, a great majority of patients are not aware of the effect of bright light therapy and its potential therapeutic effects.

3. We will not only check the blinding, but also plan to ask our subjects at day 15 whether they have tried to look up information about the devices, if yes by what means and what were their conclusions. If the blinding is not successful, we will need to treat this as an open label study.

4. The red light given is significantly dimmer (<50 lux vs 1350 lux) and not expected to provide substantial therapeutic effect. While we cannot exclude any benefit from dim red light (especially placebo response), multiple studies using dim red light as control have been positive.

5. Some authors have suggested that an inactivated negative ion generator can be used as control [10]. However, negative ion generators do not provide any light at all, making them less ideal as a control. Importantly, while there is some evidence to support the use of negative ion generators for SAD, we have not been able to find any beneficial effects for sleep specifically, making it more difficult to justify their use. Thus, we feel they are less ideal than dim red light at this time.

6. We discussed with the manufacturer of the Litebook device, and dim white light is not available.

The Litebook Company Ltd. has previously applied to the US Food and Drug Administration (FDA) for a study approval using the same device in the current proposed study. FDA concluded that this is a non-significant risk device, as it "does not meet the definition of a significant risk device under 812.3(m) of the investigational device exemptions (IDE) regulation (21 CFR 812, available on the internet at http://www.accessdata.fda.gov/scripts/cdrh/cfdocscfcfr/showCFR.cfm?CFRPart=812)" (Appendix). As such, an IDE application is neither required to be submitted nor approved by FDA for a NSR study.

Both versions of the device feature compliance monitoring capabilities, using HOBOware® data loggers embedded in each device. 'On/off' data with time/date stamp is easily uploaded to a computer for analysis via a USB port. The necessary software and USB cables are provided with the devices.

Light treatment assignment will be determined at the time of CTC registration**.** Once enrolled, study participants will be issued an active or control treatment device by a research staff for the patients to bring home (different from the blinded staff who will be performing study assessments). Subjects assigned to this device will be carefully instructed to the proper use of the light box with regard to positioning, distance, and duration of therapy:

- Positioned the device on a flat surface about an arm's length away from the subject, with the participant situated at an angle of approximately 30 degrees to the light, with their eyes at mid-fixture level. Do not directly stare at the light.

- Use the device for 30 minutes each morning within 2 hours of arising (to complete treatment before noon if possible). The devices should be used daily (7 days per week) for 15 days.
- They will be asked not to disclose to the blinded research staff which treatment device they were assigned.

Blinding: Since symptom expression is a subjective outcome, we would like to minimize ascertainment bias by using a double-blind design (i.e. research staff conducting the assessments, and the research subject). This is done by

1. The consent form stating that we are studying "two types of light, one of which is expected to be beneficial and the other is not", rather than stating our interest in the effect of bright light. While patients can see which color of light they are getting, they would not be given any information as to whether they are receiving the active intervention or control.

2. Study staff will be trained not to ask about the type/color of light. We also plan to document if at anytime there is an accidental breaking of the blinding. Study staff performing assessments will not provide the light boxes or know which arm the patients are randomized to.

3. The light box will be provided by a separate research staff not involved in study assessments. This research staff member will show patients the device, but will not provide any information regarding the specific types of light, nor its potential effectiveness.

4. We also plan to assess patients' perception whether they received the active intervention or not at Day 15. If they were not generally successful in guessing the intervention, we will consider this a blinded study. Otherwise, we will consider the blinding to be unsuccessful. Patients will also be instructed not to reveal which light they were assigned to the staff assessing their symptoms. This will improve the chances of maintaining the blinding.

The research nurse/coordinator will check the compliance of the lightbook device usage during weekly telephone call or in person visit.

Unblinding Procedure:

1. The Statistician and the investigational pharmacist will have access to the codes/assignments.

2. The codes will be revealed only If there is a safety issue and the treating physician needs to be aware of the treatment assignment.

3. The PI should be contacted regarding the patient's circumstances.

4. Prior to unblinding a patient, the investigator or research team will inform the IND Office Medical Monitor.

5. The Investigator will then give permission for the unblinding to the statistician and the investigational pharmacist.

6. The investigator or research team will notify the DSMB and IRB of the unblinding.

E.2 Methylphenidate Treatment.

MP is very well tolerated when used in cancer patients, when used long-term in attention deficit disorder, and when used in the management of depression. A dose of 5 mg orally administered twice daily will be used. The last dose of the twice a day regimen should be prior to 3pm and the interval between doses should be at least 2 hours. This dose regimen has been well tolerated in these trials and in the current ongoing trial of methylphenidate for the treatment of

fatigue (a total 190 patients are enrolled to date). We will instruct patients that methylphenidate may be taken without regards to meals and stored at room temperature. Patients will also receive a copy of the FDA-approved Medication Guide specific to methylphenidate.

Contraindications. Marked anxiety, tension, and agitation are contraindications to methylphenidate, since the drug may aggravate these symptoms. Methylphenidate is also contraindicated in patients' known to be hypersensitive to the drug, in patients with glaucoma, motor tics or with family history or diagnosis of Tourette's syndrome. Methylphenidate is contraindicated during treatment with monoamine oxidase inhibitors, and also within a minimum of 14 days following discontinuation of a monoamine oxidase inhibitor. Other contraindications include thyrotoxicosis, severe angina pectoris, and uncontrolled hypertension.

Drug interactions. The safety of using methylphenidate in combination with clonidine or other centrally acting alpha-2 agonists has not been systematically evaluated. Methylphenidate may inhibit the metabolism of coumarin anticoagulants, anticonvulsants (Phenobarbital, diphenylhydantione, primidone), phenylbutazone, and tricyclic drugs (imipramine, clomipramine, desipramine). Downward dosage adjustments of these drugs may be required when given concomitantly with methylphenidate. Serious adverse events have been reported in concomitant use with clonidine, although no causality for the combination has been established.

Adverse reactions. Methylphenidate Side Effects

It is not well known how often the side effects of methylphenidate may occur.

chest pain due to heart trouble
irregular heartbeat
abnormal heart sound
fast, slow, or extra heartbeats
bleeding in the brain
blocked blood vessel in the brain (possible stroke)
stroke
blood vessel inflammation (possible bleeding and/or bruising)
low blood pressure (possible dizziness/fainting)
high blood pressure
blood vessel disorder causing painful, cold, numb, and discolored fingers and/or toes
hallucinations (seeing or hearing things that are not there)
seizure
mood changes (such as anger, anxiety, agitation, depression, aggressive behavior, mood swings, irritability, nervousness, and/or restlessness)
confusion
dizziness
fatigue
fever
headache
heightened alertness
difficulty sleeping
mood disorder with extremes of happiness and sadness
obsessive-compulsive disorder
neuroleptic malignant syndrome (possible high blood pressure, muscle stiffness, and/or fever)
Tourette's syndrome (uncontrolled speech and/or muscle movements)
physical tension
psychosis (loss of contact with reality)
tremors
hair loss (partial or total)
allergic skin reaction
shedding and scaling of the skin (possible fatal loss of bodily fluids)
increased sweating
skin rash
hives
painful menstruation
decreased sex drive
impotence
low red, white, and platelet counts
abdominal pain
loss of appetite
constipation
diarrhea
upset stomach
nausea
vomiting
weight loss
dry mouth
abnormal liver tests (possible liver damage)
liver failure
stunted growth
joint pain
uncontrolled movements
muscle tightness
abnormal sensation (such as pins and needles)
dry eyes
pupil dilation (possible light sensitivity)
vision problems (such as double vision and blurry vision)
cough
difficulty breathing
sore throat
throat pain
runny nose
accidental injury related to physical activity
life-threatening allergic reaction (such as difficulty breathing, low blood pressure, and/or organ failure)
allergic reaction (possible swelling (ear),blisters, skin peeling, skin rash)
grinding or clenching of teeth

Methylphenidate may cause low blood cell counts (red blood cells, platelets, and white blood cells):

- A low red blood cell count (anemia) may cause difficulty breathing and/or fatigue. You may need a blood transfusion.
- A low platelet count increases your risk of bleeding (such as nosebleeds, bruising, stroke, and/or digestive system bleeding). You may need a platelet transfusion.
- A low white blood cell count increases your risk of infection (such as pneumonia and/or severe blood infection). Infections may occur anywhere and become life-threatening.

Drug Dependence. Methylphenidate has been abused and it has addictive potential. Our group has conducted five trials of methylphenidate, and we are not aware of any cases of abuse in cancer patients when treated with this drug. However, this drug has been abused by other patient populations, and therefore, patients will be informed about this risk and carefully monitored.

Information regarding abuse and all other side effects will be part of the research nurse-training program.

Storage Information. Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature]. Protect from light.

All patients will be dispensed methylphenidate or placebo by the Investigational Pharmacy at MDACC. The medication will be provided free of charge.

Disposal Information Any used methylphenidate or placebo will be returned to the research nurse or coordinator. The research nurse or coordinator will then return the unused methylphenidate or placebo to Investigational Pharmacy and they will then dispose of the unused portion according to MDACC policy.

Compliance for the use of the study drug will be documented by the research nurse/coordinator during their weekly telephone call or with an in person visit.

E.3 CBT.

Patients receiving CBT will receive 3 sessions between Baseline and Day 14+/- 3 days (all by phone unless clinic time permits the first session to be in person); each session will last approximately 30 minutes each. Sessions will be led by a Master's degree level counselor under Dr. Carmack's supervision. The first session will cover sleep education and sleep hygiene. The second session will focus on cognitive strategies to target negative thoughts that could be contributing to or exacerbating sleep problems. The final session will cover relaxation training including diaphragmatic breathing and guided imagery. Patients will be provided with a CD of relaxation exercises and will be encouraged to practice them daily for at least 10 minutes. Patients will be provided with logs to monitor sleep, as well as record practice of the cognitive and behavioral skills taught in each session. These logs will be reviewed at each session. Telephone counseling sessions will be audiotaped for quality control. Dr. Carmack will review a random sample of audiotaped sessions to verify coverage of the weekly review, teaching of cognitive-behavioral skills, skills practice and discussion, and assignment of homework for practice.

We do not expect any serious adverse events or adverse events associated with any of the treatment combinations. Any adverse event or serious adverse event deemed treatment-related will trigger will be reviewed by MD Anderson Cancer Center's Data Monitoring Safety Board and an assessment of whether one or more treatment combinations should be halted to ensure patient safety.

E.4 Melatonin: The dose of 20mg orally and the modality of administration at bed time has been chosen because it was found to be effective based on prior studies [57] for fatigue related symptoms of sleep, cachexia and also well tolerated based on prior studies (15-18) in our RCT study (NCT00513357).

All patients will be dispensed melatonin or placebo by the Investigational Pharmacy at MDACC. The medication will be provided free of charge.

Contraindications: Melatonin may cause drowsiness. Patients are not to drive, operate machinery, or do anything else that could be dangerous until you know how you react to this product. Using this product alone, with certain other medicines or with alcohol may lessen their ability to drive or to perform other potentially dangerous tasks. Patients will be instructed to avoid drinking alcohol or taking other medications that cause drowsiness (eg, sedatives, tranquilizers)

while taking this product. This product will add to the effects of alcohol and other depressants. Patients will be asked to consult a pharmacist if they have questions about which medicines are depressants. This product has not been approved by the Food and Drug Administration (FDA) as safe and effective for any medical condition. The long-term safety of dietary supplements is not known. PREGNANCY and BREAST-FEEDING: Patients will be advised to not use this product if you plan to become pregnant. It may have a contraceptive effect. Melatonin is not recommended for use during pregnancy. Because of the potential risk to the infant, breast-feeding while using this product is not recommended.

Adverse Reactions: Melatonin Side Effects

It is not well known how often the side effects of melatonin may occur.

headache	giddiness (abnormal	depression
drowsiness	excitement)	nausea
mood swings	worsening symptoms of existing depression	infection

Storage Information: Store at room temperature away from heat, moisture, and light.

Adherence:
Patients with similar characteristics to those of patients we will admit to the study have demonstrated strong adherence to assessments of the same duration in studies conducted by our group [21,22,52,53,63]. These assessment tools have been validated and are reliable for use in the collection and analysis of data. Also, patients in this study will not undertake time-intensive radiologic tests such as MRIs or drug pharmacokinetic studies, which are a common part of cancer clinical trials. This will help in completing the study in a timely manner and minimize attrition.

Subject Burden: The total time to complete the assessments will be approximately 30 minutes. Many patients in our supportive care clinic are successfully prescribed CBT, light therapy and medications with excellent compliance (and therefore presumably low burden). Several aspects of the study design (e.g., scheduling around RT, using telephone interventions, administering methylphenidate on a simple dosing schedule) are also intended to minimize patient burden. Prior fatigue treatment trials conducted by our group have demonstrated strong adherence to assessments of the same duration [21,22,52,53,63]. A similar CBT trial by our group [59-62], found excellent adherence of approximately 83% at 6 months and 84% at 12 months. As the counseling is done at patients' home and on their own time schedule, we anticipate excellent adherence. This is based on similar current ongoing trial funded by NIH grant NR010162, which has a telephone counseling intervention with an adherence of 85% in 160 participants accrued to date. The MP schedule and dosing proposed here have been used in prior fatigue trials and in the current ongoing trial and it has been found to be well tolerated.

III. Study Assessments

i. Demographic Variables (APPENDIX A).

Include patient's birth date, sex, marital status, ethnicity, education, job status, primary cancer, cancer treatment (s) within the last year, (surgery, chemotherapy, immunotherapy, or RT), and medications.

ii. Outcome Measures:

a) PSQI (APPENDIX B) The PSQI is a 19-item questionnaire that is an effective instrument in measuring the quality and patterns of sleep[64].It differentiates "poor" from "good" sleep by measuring seven areas: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction over the last month. Each area is rated from 0-3 with the higher score reflecting more severe sleep complaints. The addition of all scores permits the analysis of the participant's overall sleep experience. The PSQI can be used for both an initial assessment and ongoing comparative measurements across all healthcare settings. The PSQI has internal consistency and a reliability coefficient (Cronbach's alpha) of 0.83 for its seven components. Numerous studies using the PSQI have supported high validity and reliability. The PSQI global score ranges from 0 to 21, with a score of 5 or greater indicating significant sleep disturbance. We will define response in this study using a reduction in PSQI global score at day 15 assessments of 3 as compared to baseline.

b) Functional Assessment of Chronic illness Therapy- Fatigue (FACIT-F): The FACIT-F forms the core of the FACT measurement system and consists of subscales assessing physical well being (PWB-7 items), social/family well being (SFWB-7 items), emotional well being (EWB-6 items), functional well being (FWB-7 items), and relationship with doctor (RWD-2 items). The FACIT-F yields a total score, as well as individual subscale scores, with higher scores reflecting better quality of life(66). The FACIT-F fatigue subscale has been used primarily in cancer patients to measure fatigue [66].

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).

c) Functional Assessment of Cancer Therapy: General (FACT-G): FACIT-F is a well-validated quality-of-life instrument widely used for the assessment of cancer-related fatigue and sleep disturbances in clinical trials. It consists of 27 general quality-of-life questions divided into four domains (physical, social, emotional, and functional). According to the scoring manual, the negatively worded items on the FACT were reverse scored so that the higher scores indicated more positive health states. Test-retest reliability coefficients for the FACIT-F subscale have ranged from 0.84–0.90 23. This scale has been shown to have strong internal consistency ($\alpha = 0.93$–0.95). It has a sensitivity of 0.92 and specificity of 0.6923.

Depression and anxiety:

d) Depression and anxiety symptoms will be assessed by using the 14-item HADS (APPENDIX C) [67] questionnaire, which asks patients to underline the statement that most closely matches how they felt in the previous week. This questionnaire is valid and reliable in a number of clinical situations and has been widely used in cancer patients.

Other common symptoms:

e) *The Edmonton Symptom Assessment Scale (ESAS)* (APPENDIX D) [68] measures 10 common symptoms experienced during the previous 24 hours (pain, fatigue, nausea, depression, anxiety, drowsiness, shortness of breath, appetite, sleep, and feeling of well-being); this questionnaire has been found to be valid and reliable in cancer populations.

Physical activity:

f) *Actigraphy:* The Actiwatch 2 portable recorder (Mini Mitter Company, Inc. A Respironics, Inc., OR, USA) is a small wrist-worn device, sized 1 X 2 X 4 cm, containing an accelerometer that is optimized for highly effective sleep-wake inference from wrist activity that has been previously validated [25,42,69,70].

Data will be collected in 1-min epochs and transferred, via an interface, to a computer to be analyzed. Actigraphy will be analyzed for Days 1 to 15 (+/- 3 days).

Aim 3. To determine the safety of MMT (type, frequency, and severity of the adverse events).

g.) Insomnia Severity Index: is a seven item questionnaire designed to evaluate insomnia severity on the basis of difficulties falling asleep, night-time awakening, early morning awakenings, impairment of daytime functioning due to sleep problems, noticeability of impairments, distress or worry caused by sleep difficulties, and dissatisfaction with sleep. Each item is rated using a five-point likert scale ranging from 0 (not at all) to 4 (very much), for a total score ranging from 0-28. The ISI has adequate psychometric properties and is sensitive to measure treatment response (71, 72).

h.) The Memorial Delirium Assessment Scale (MDAS) is a clinician-rated, 10-item rating scale used to assess the severity of delirium over the past several hours. Each item is scored from 0 to 3 depending on its intensity and frequency (possible range of total score, 0-30). The 10 items are anchored with statements reflecting the severity or intensity of the symptom and were reviewed by experienced clinicians to ensure ease of administration and the ability to generate accurate (reliable) ratings. The resulting scale, which requires approximately 10 minutes to administer, integrates behavioral observations and objective cognition testing. When items cannot be administered, scores can be prorated from the remaining items to an equivalent 10-item score. The MDAS is highly correlated with existing measures of delirium and cognitive impairment, yet offers several advantages over these instruments for repeated assessments, which are often necessary in clinical research. The cut of 13 has been used based on studies in cancer and non-cancer palliative care population (73, 74).

i.) Global Symptom Evaluation. This instrument is to estimate the minimal important difference in symptoms before treatment and after treatment. Patients will be asked about their symptoms (worse, about the same, or better) after starting study treatment. If their answer is better, patients will be asked to rate how much better their symptoms are (almost the same, hardly any better at all, a little better, somewhat better, moderately better, a good deal better, a great deal better, a very great deal better). If their answer is worse, patients will be asked to rate how much worse their symptoms are (almost the same, hardly worse at all, a little worse, somewhat worse, moderately worse, a good deal worse, a great deal worse, a very great deal worse). This evaluation will be performed on day 15 and day 29**.**

CBT, Light Therapy, Melatonin and MP have been used in prior trials by our team and found to be safe. We do not expect any serious adverse events or adverse events associated with any of the treatment combinations. However, we will monitor the safety of the interventions.

***MP and Melatonin*:**
Instructions for the administration of MP and Melatonin will be provided by the research nurse/coordinator. If the patients have questions in regards to administration and side effects, the nurse will answer and refer further questions to the PI (S.Y) or co-PI (E.B). The side effects will be monitored as per the toxicity assessment schedule at Day 8, 15, 29, and 45 (or 1 month after the last MP or Melatonin dose.

***CBT*:**
This treatment plan has been successfully and safely used in cancer patients and in prior trials by our team [59-62]. However, in the event of severe emotional distress or mood disturbance, referral to the

psychiatry team will be made. We will monitor for any suicidal thoughts or ideation. The assessment of mood will be conducted during each CBT patient session.

M. D. Anderson Cancer Center's Data Monitoring Safety Board will review any adverse event or serious adverse event that is suspected to be treatment-related to ensure patient safety.

Table 4.

ASSESSMENTS	BASELINE (± 1 week)	DAY 3 (± 3)	DAY 8 (± 3)	DAY 15 (± 3)	Day 29 F/U (± 1 week)	Day 45 Post Treatment F/U or 30 Days After Last Treatment (± 5)
History/Physical Exam	X				X*	
Zubrod score	X	X*			X*	
Medication review	X	X*	X*	X*	X*	
Edmonton Symptom Assessment Scale (ESAS)	X	X*	X*	X*	X*	
FACIT-F, Functional Assessment of Cancer Therapy - General (FACT-G) ,HADS, PSQI , Insomnia Severity Index	X	X*	X*	X*	X*	
Light therapy compliance evaluation	X		X*	X*		
Cognitive behavioral therapy	X		X*	X*		
Actigraphy	X**					
Hematology/chemistry (including Calcium and glucose if not done within the past 15 days) if not done in the past 4 months)	X***				X	
Toxicity evaluation	X	X*	X*	X*	X*	X*
Blinding Check				X*		
Pregnancy Testing (for women of child bearing age)	X					
Memorial Delirium Assessment Scale (MDAS)	X					
Global Symptom Evaluation				X	X*	

*In person or telephone evaluation
**1st week after baseline assessment and 1 week prior to the primary end point
***Hematology at Baseline only

Monitoring plan:
All Grade≥ 2 toxic effects reported by patients in this trial will be evaluated by the principal investigator and treating physician or by an attending physician if the PI is not available, to determine whether the toxic effects were due to a study intervention. We will monitor for safety according to the procedures detailed in the section. Any treatment or treatment combination that is determined by the PI to have caused a significant toxicity (significant toxicity and toxic effects are defined as any Grade 3 or 4 toxicity that is intervention-related) in more than 1 of the first 6 patients to whom the treatment or treatment combination was administered (even if administered with other treatments) will be dropped from the study design. We will use the CTCAE version 4.0. We will collect adverse events (including abnormal values) according to the Recommended Adverse Event Recording Guidelines on page 22. If a treatment or treatment combination is administered to more than 6 patients (possibly in conjunction with other treatments), it will be dropped from the design if it is determined by the PI to be responsible for 2/6, 3/9, 4/12, 5/15, 6/18, 7/21, 8/24, 9/27, 10/30, 11/31 toxic effects. These stopping boundaries correspond to dropping treatment combinations from the study if the posterior probability that they result in greater than 33% DLT exceeds 0.5 when a non-informative (Jeffreys) prior is assumed for this probability a priori. For example, if it happens that the first two patients enrolled in the trial are assigned to receive light therapy and melatonin + MP, and if both patients experience grade 3 toxic effects that the PI determines were due to the light therapy, then all treatment combinations involving light therapy would be dropped from the factorial design because the 2/6 stopping boundary would have been reached for this treatment combination. The following toxicities are confirmed to count towards the stopping rule: dizziness, anorexia, restlessness, and tachycardia.

The determination of whether a toxic effect (grade 3, 4) was due to the symptom treatment combination received by the patient (rather than by the primary chemotherapy agent or radiation therapy) will be made by the PI in consultation with the treating physician. In addition, toxic effects (grade 3, 4) will be counted against all higher-order treatment combinations whenever at least 1 toxic effect is observed for a specified treatment. For example, if (at least) one treatment toxic effect (grade 3, 4) is attributed to a patient who receives intervention melatonin and MP, then toxic effects observed in patients who receive intervention melatonin, CBT, and MP will also be attributed toward those experiencing toxic effects with the combination of intervention melatonin and MP alone. Patient toxic effects (grade 3, 4) will also be counted against lower-order treatment combinations when the principal investigator and treating physician determine that the toxic effect (grade 3, 4) could have been the result of one of the component treatments alone. For example, grade 3 diarrhea observed in a patient assigned to melatonin and CBT might also be counted against the single-agent treatment of cognitive behavioral therapy. Any adverse event or serious adverse event deemed treatment-related will trigger a review of the protocol and an assessment of whether one or more treatment combinations should be halted.

Unblinding of the Light therapy, Melatonin and Methylphenidate arm: If unexpected serious side effect attributable to the study treatment occurs the blind code will be broken), patients will be taken off study, and appropriate interventions will be provided to the patient.
Adverse events will be documented in the medical record and entered into the case report form according to the Recommended AE recording guidelines for Phase II protocols.

The Investigator or physician designee is responsible for verifying and providing source documentation for adverse events and assigning the attribution for each event for all subjects enrolled on the trial. PDMS will be used as the electronic case report form (CRF) for this protocol and protocol specific data will be entered into PDMS.

Recommended Adverse Event Recording Guidelines					
Attribution	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Unrelated	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Unlikely	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Possible	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Probable	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Definitive	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III

IV. Statistical Considerations:

Factorial Randomization:

A key component of this proposal is the use of a randomized factorial design to rapidly assess the efficacy of a large number of potential treatment(s) and treatment synergies [28,29]. This design exploits the fact that treatments evaluated during this project are known a priori to have neither minimal toxic effects nor toxic interactions with each other. In this sense, this trial differs from most clinical trials; in general, cancer treatments are associated with significant toxic effects, and these effects increase when the treatments are administered simultaneously with other potentially toxic treatments. Because the symptom treatments considered in this project do not share these features of standard cancer therapies, it will be possible to assign multiple treatments to the same patients. This in turn will allow us to assign treatments according to a randomized version of a factorial design. The primary advantage of the factorial design derives from the efficiency with which main treatment effects and second-order interactions between treatments can be evaluated. Assuming that there are *n* patients enrolled into the

trial, *n/2* patients will be assigned to every treatment, and the remaining *n/2* patients will be available to serve as controls. Ignoring higher-order interactions between treatments, this means that the main effects of each treatment will be estimable with the same precision as they would be in a two-arm trial involving only that treatment. Similar gains in efficiency will also be accrued in evaluating second-order synergies among treatments.

Sixty-four patients will be randomized equally among the 8 possible treatment combinations, 8 per arm. Randomized block allocation with a block size of 8 will be used to ensure that the first 8 patients include 1 with each treatment combination. The randomization will be performed by Dr. Kenneth R. Hess in the Department of Biostatistics in the Division of Quantitative Sciences. There will be a primary and a secondary statistical contact to ensure that the process proceeds smoothly. The trial will be placebo-controlled. Because 8 patients are required for a single replication of the factorial design with 3 treatments, a total of 64 patients will be used in this trial.

	Patient							
Intervention	1	2	3	4	5	6	7	8
Light Therapy	0	X	0	0	X	X	0	X
Melatonin	0	0	X	0	X	0	X	X
Methylphenidate	0	0	0	X	0	X	X	X
	Patient							
Intervention	9	10	11	12	11	14	15	16
Light Therapy	0	X	0	0	X	X	0	X
Melatonin	0	0	X	0	X	0	X	X
Methylphenidate	0	0	0	X	0	X	X	X
	Patient							
Intervention	17	18	19	20	21	22	23	24
Light Therapy	0	X	0	0	X	X	0	X
Melatonin	0	0	X	0	X	0	X	X
Methylphenidate	0	0	0	X	0	X	X	X
	Patient							
Intervention	25	26	27	28	29	30	31	32
Light Therapy	0	X	0	0	X	X	0	X
Melatonin	0	0	X	0	X	0	X	X
Methylphenidate	0	0	0	X	0	X	X	X

	Patient							
Intervention	33	34	35	36	37	38	39	40
Light Therapy	0	X	0	0	X	X	0	X
Melatonin	0	0	X	0	X	0	X	X
Methylphenidate	0	0	0	X	0	X	X	X
	Patient							
Intervention	41	42	43	44	45	46	47	48
Light Therapy	0	X	0	0	X	X	0	X
Melatonin	0	0	X	0	X	0	X	X
Methylphenidate	0	0	0	X	0	X	X	X
	Patient							
Intervention	49	50	51	52	53	54	55	56
Light Therapy	0	X	0	0	X	X	0	X
Melatonin	0	0	X	0	X	0	X	X
Methylphenidate	0	0	0	X	0	X	X	X
	Patient							
Intervention	57	58	59	60	61	62	63	64
Light Therapy	0	X	0	0	X	X	0	X
Melatonin	0	0	X	0	X	0	X	X
Methylphenidate	0	0	0	X	0	X	X	X

Statistical Analyses Plan:

Aim 1. The primary outcome variable for this study is the change in PSQI score. The value of this variable for patient *i* is denoted as *fci*. (PSQI change). The primary goal of this study is to assess (by PSQI score change) the three treatments used in this study(without the need of a second, larger study), but if one or more treatment combinations do appear effective, a larger study will be designed using estimates of intersubject variability and treatment efficacies estimated from this design. Estimates of treatment effects and combinations of treatment effects will be obtained by using standard linear regression techniques in which the change in PSQI values are regressed on indicator variables that represent treatment combinations that received 3 main effects for the primary treatments, 3 two-way interaction terms for each combination of two treatments, and 1 three-way interaction effects, which will

be included in the linear regression model. The resulting regression model can be expressed as follows:

$$fc_i = \beta_0 + \beta_1 Ind(T_1) + \beta_2 Ind(T_2) + ... + \beta_{1,2} Ind(T_1, T_2) + ... + \beta_{1,2,3} Ind(T_1, T_2, T_3) + \varepsilon_i$$

In this equation, $Ind(T_1)$ denotes assignment of patient i to treatment 1, and β_1 denotes the mean effect of treatment 1 on a randomly selected patient's PSQI score. $Ind(T_1, T_2)$ denotes the assignment of treatments/interventions 1 and 2 to patient i, and $\beta_{1,2}$ represents the average effect of this treatment on the *f*ci. score. Similar notation applies to other treatment combinations. Note that the parameter $\beta_{1,2}$ represents the additional or synergistic treatment effect of treatments 1 and 2 when these treatments are assigned together, over and above the effects that these treatments have alone (i.e., $\beta_1 + \beta_2$). The term ε_i denotes random error in reported fci values, which is normally distributed with mean 0 and variance σ^2 equal to 11.5^2 = 132.

Sample size justification:
In this study, we will assess three treatments (Light therapy, Melatonin, MP) and their placebo treatments with CBT in 8 replications of a complete factorial design. A total of 32 patients will receive each primary treatment (Light therapy, Melatonin, MP) and 32 will not. Within each group of 32, the allocation of the other treatment combinations will be balanced so that the additive effects of the other treatments cancel out; this means that we will be able to make comparisons between each of the 3 main treatments with similar level of accuracy as if we had performed 3 trials, each with 64 patients. In other words, the variance of the estimate of the main treatment effects is similar as if the trial had been performed with 64 patients, 32 receiving treatment and 32 receiving placebo. For the three second-order interactions, comparisons will have similar error variance that would have been estimated with 16 patients assigned to the two-drug combination and 48 to placebo. The variance of the estimate of the effect of the three-drug combination will be similar to the variance that would be estimated if 8 of 64 patients were receiving the three-drug combination and 56 were receiving the placebo. Thus data collected from this novel randomized factorial design will enable us to assess the three treatments used in this study(without the need of a second, larger study), but if one or more treatment combinations do appear effective, a larger adaptive randomized study will be designed using estimates of intersubject variability and treatment efficacies estimated from this design.

Although the goal of this trial is to obtain preliminary estimates of the efficacy of various treatment combinations, for completeness we have provided a limited table of operating characteristics below. The entries in the table 6 represent the power that we would have in detecting treatment effects of the given magnitude based on the factorial design alone, assuming that no treatments are dropped from the study design due to feasibility considerations. All analyses are based on intent-to-treat, and patients dropping out before administration of the final PSQI score we would use the most recent PSQI score (even if it is baseline) as the estimated final score. All entries in the table are based on an assumption that tests for significance are performed at the 5% level.

Table 5: Power to detecting treatment effects of the given magnitude based on the factorial design

Treatment	**Power**
1) $\beta_1 = 5$	12%

2) $\beta_1 = 7$ 19%

3) $\beta_1 = 10$ 33%

4) $\beta_1 = 12$ 44%

5) $\beta_1 = 15$ 62%

6) $\beta_{1,2} = 5$ 9%

7) $\beta_{1,2} = 7$ 12%

8) $\beta_{1,2} = 10$ 19%

9) $\beta_{1,2} = 12$ 25%

10) $\beta_{1,2} = 15$ 37%

11) $\beta_{1,2,3} = 5$ 7%

12) $\beta_{1,2,3} = 7$ 8%

13) $\beta_{1,2,3} = 10$ 12%

14) $\beta_{1,2,3} = 12$ 15%

15) $\beta_{1,2,3} = 15$ 21%

Aim 2. As a secondary objective of this project, we will perform exploratory data analyses to examine associations between patients' change in PSQI score and the secondary measures of Insomnia Severity Index, FACIT-F, HADS, ESAS, and Actigraphy. Since each of these variables is also continuous and measured at the same points in time, we will perform multivariate regression analyses to determine the predictive relationship of each of these variables on PSQI and change in PSQI scores. With use of actigraphy, we would analyze differences between participants receiving the MMT or the placebo treatment. This analysis will be based on fitting mixed effect linear models with actigraphy data as the response variables, and treatment intervention, demographic variables, and treatment site as independent variables.

The primary analyses will include only information from baseline and Day 15, but other analyses will include information from all three time points (baseline Day 8, and Day 15). Finally, we will expand the regression equation to include patient demographic information (i.e., age, ethnicity, and baseline ESAS symptoms and referral site) to determine whether these variables are significant as predictors of change in the PSQI score. Note that because our primary outcome variable is change in the PSQI score, additive effects of the demographic and site variables can be expected to approximately cancel (i.e., if gender-female has the effect of adding c units to a PSQI score, by taking differences within subjects, the constant c cancels out). Similar comments apply also to potential referral site effects. Similarly we will summarize the PSQI change and secondary outcomes as detailed above at Day 29 follow-up.

Feasibility and Adherence: Study treatments will be deemed to be feasible if ≥60% of patients assigned to each treatment are adherent. Adherence to the CBT will be defined as the ability to complete ≥60% of the scheduled intervention. Adherence to the each of the medication arms will be defined as the ability to complete 60% of the scheduled study medication (methylphenidate, melatonin) or placebo regimen. Adherence to the Light therapy or its Placebo will be defined as the ability to complete ≥60% of the scheduled intervention. Logistic regression analyses will be used to explore factors related to adherence for treatments that are dropped from study.

Aim 3. Information about toxic effects and tolerability will be summarized.

V. Serious Adverse Event Reporting:
An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

- Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.
- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Serious Unanticipated Adverse Events for Drugs and Devices". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).
- All life-threatening or fatal events, that are unexpected, and related to the study drug, must have a written report submitted within 24 hours (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.
- Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.

- Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose of drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.
- Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.

Reporting to FDA:

- Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.

It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

VI. Future studies:
At the end of this study, we will have obtained evidence on the combined interventions most likely to be effective for the management of SD, patient adherence, and side effect profiles. The magnitude and variance of treatment effects estimated from the outcomes of this trial will be used to design future trials, if needed, between promising treatments identified during this trial. In addition, the effect sizes and interpatient variability of treatment effects estimated during this trial will be used to design future trials for similar treatments in other populations of cancer patients. In addition, this study will provide preliminary data for further studies exploring the biological and psychosocial mechanisms mediating SD.

VII. Statement of Cancer Relevance:
SD is the most common complaint of patients with Advanced Cancer. SD has detrimental effects on patients' physical, psychological, social, occupational functioning and ability to continue cancer treatment. However there are limited treatment options for SD. Preliminary data by our research team and others suggest that Cognitive behavioral therapy Melatonin and Methylphenidate play important role in reduction of SD. In this study, we propose the novel use of CBT in addition to multidimensional treatment combinations, MMT [Light Therapy, Melatonin and MP] to target the multifactorial SD in a well-defined population. An effective low cost low risk easily accessible treatment for SD would benefit a large number of cancer patients.

References

1. Koopman C, Nouriani B, Erickson V, et al. Sleep disturbances in women with metastatic breast cancer. Breast Journal. 2002;8(6):362-370.
2. Berger AM, Parker KP, Young-McCaughan S, et al. Sleep/wake disturbances in people with cancer and their caregivers: state of the science. Oncology Nursing Forum. 2005;32(6):E98-126.
3. Lianqi L, Ancoli-Israel S. Sleep Disturbances in Cancer. Psychiatric Annals. 2008;38(9):627-634.
4. Yennurajalingam.S, Chisholm.G, Palla S. L., Bruera. Sleep disturbance in patients with advanced cancer: Frequency and factors associated with response to specialist-based outpatient supportive care. J Clin Oncol 29: 2011 (suppl; abstr 9069).
5. Redwine L, Hauger RL, Gillin JC, Irwin M. Effects of Sleep and Sleep Deprivation on Interleukin-6, Growth Hormone, Cortisol, and Melatonin Levels in Humans. Journal of Clinical Endocrinology & Metabolism. October 1, 2000 2000;85(10):3597-3603.
6. Davidson JR, MacLean AW, Brundage MD, Schulze K. Sleep disturbance in cancer patients. Social Science & Medicine. 2002;54(9):1309-1321.
7. Lamberg L. Sleep Disorders, Often Unrecognized, Complicate Many Physical Illnesses. JAMA: The Journal of the American Medical Association. November 1, 2000 2000;284(17):2173-2175.
8. Sateia M, Lang B. Sleep and cancer: Recent developments. Current Oncology Reports 2008;10:309-18.
9. Desan PH, Weinstein AJ, Michalak EE, et al. A controlled trial of the litebook light-emitting diode (LED) light therapy device for treatment of seasonal affective disorder (SAD). BMC Psychiatry. 2007;7:38.
10. Tuunainen A, Kripke DF, Endo T. Light therapy for non-seasonal depression. Cochrane Database Syst Rev. 2004;(2)(2):CD004050.
11. Terman M, Lewy AJ, Dijk DJ, Boulos Z, Eastman CI, Campbell SS. Light treatment for sleep disorders: Consensus report. IV. sleep phase and duration disturbances. J Biol Rhythms. 1995;10(2):135-147.
12. Ancoli-Israel S, Martin JL, Kripke DF, Marler M, Klauber MR. Effect of light treatment on sleep and circadian rhythms in demented nursing home patients. J Am Geriatr Soc. 2002;50(2):282-289.
13. Golden RN, Gaynes BN, Ekstrom RD, et al. The efficacy of light therapy in the treatment of mood disorders: A review and meta-analysis of the evidence. Am J Psychiatry. 2005;162(4):656-662.
14. Buscemi N, Vandermeer B, Pandya R, Hooton N, Tjosvold L, Hartling L, Baker G, Vohra S, Klassen T. Melatonin for Treatment of Sleep Disorders. http://www.ahrq.gov/clinic/epcsums/melatsum.htm. Accessed as of Jan 2012.
15. Garfinkel D, Laudon M,Nof D, Zisapel N. Improvement of sleep quality in elderly people by controlled release melatonin. Lancet.1995,Vol/Iss/Pg.346/89743(541-544).
16. Oldani A Ferini-Strambi L Zucconi M Stankov B Fraschini F Smirne S Melatonin and delayed sleep phase syndrome:ambulatory polygraphic evaluation. Neuroreport. 6(1):132-4 1994 Dec 30

17. Zhdanova IV Wurtman RJ Lynch HJ Ives JR Dollins AB Morabito C Matheson JK Schomer DL Sleep-inducing effects of low doses of melatonin ingested in the evening. Clinical Pharmacology and Therapeutics. 57(5): 552-8, 1995 May.
18. Kooij JJ, Middelkoop HA, van Gils K, Buitelaar JK. The effect of stimulants on nocturnal motor activity and sleep quality in adults with ADHD: an open-label case-control study. J Clin Psychiatry. 2001 Dec;62(12):952-6.
19. Sobanski E, Schredl M, Kettler N, Alm B. Sleep in adults with attention deficit hyperactivity disorder (ADHD) before and during treatment with methylphenidate: a controlled polysomnographic study. Sleep. 2008 Mar;31(3):375-81.
20. Bruera E, Driver L, Barnes EA, et al. Patient-Controlled Methylphenidate for the Management of Fatigue in Patients With Advanced Cancer: A Preliminary Report. Journal of Clinical Oncology 2003;21:4439-43.
21. Bruera E, Valero V, Driver L, et al. Patient-Controlled Methylphenidate for Cancer Fatigue: A Double-Blind, Randomized, Placebo-Controlled Trial. Journal of Clinical Oncology 2006;24:2073-8.
22. Savard J, Simard S, Ivers H, Morin CM. Randomized Study on the Efficacy of Cognitive-Behavioral Therapy for Insomnia Secondary to Breast Cancer, Part I: Sleep and Psychological Effects. Journal of Clinical Oncology 2005;23:6083-96.
23. Espie CA, Fleming L, Cassidy J, et al. Randomized Controlled Clinical Effectiveness Trial of Cognitive Behavior Therapy Compared With Treatment As Usual for Persistent Insomnia in Patients With Cancer. Journal of Clinical Oncology 2008;26:4651-8.
24. Ancoli-Israel S. Recognition and Treatment of Sleep Disturbances in Cancer. Journal of Clinical Oncology. December 10, 2009 2009;27(35):5864-5866.
25. Epstein DR, Dirksen SR. Randomized trial of a cognitive-behavioral intervention for insomnia in breast cancer survivors. Oncology Nursing Forum. 2007;34(5):E51-59.
26. Morin CM, Vallières A, Guay B, et al. Cognitive Behavioral Therapy, Singly and Combined With Medication, for Persistent Insomnia. JAMA: The Journal of the American Medical Association. May 20, 2009 2009;301(19):2005-2015.
27. Fisher. R.A. The design of experiments (1935).
28. Wu J, and Hamada M. Experiments: Planning, Analysis, and Parameter Design
29. Mystakidou K, Parpa E, Tsilika E, et al. Sleep quality in advanced cancer patients. Journal of Psychosomatic Research. 2007;62(5):527-533.
30. Miller, A.H., et al., Neuroendocrine-immune mechanisms of behavioral comorbidities in patients with cancer. J Clin Oncol, 2008. 26(6): p. 971-82.
31. Vgontzas, A.N., et al., Circadian interleukin-6 secretion and quantity and depth of sleep. J Clin Endocrinol Metab, 1999. 84(8): p. 2603-7.
32. Morgan, K., Daytime activity and risk factors for late-life insomnia. J Sleep Res, 2003. 12(3): p. 231-8.
33. Opp, M.R., Cytokines and sleep. Sleep Med Rev, 2005. 9(5): p. 355-64.
34. Vgontzas, A.N., et al., Adverse effects of modest sleep restriction on sleepiness, performance, and inflammatory cytokines. J Clin Endocrinol Metab, 2004. 89(5): p. 2119-26.
35. Patel, S.R., et al., Sleep duration and biomarkers of inflammation. Sleep, 2009. 32(2): p. 200-4.
36. Savard, J. and C.M. Morin, Insomnia in the context of cancer: a review of a neglected problem. J Clin Oncol, 2001. 19(3): p. 895-908.

37. Grond, S., et al., Prevalence and pattern of symptoms in patients with cancer pain: a prospective evaluation of 1635 cancer patients referred to a pain clinic. J Pain Symptom Manage, 1994. 9(6): p. 372-82.
38. Montgomery, P. and J. Dennis, Cognitive behavioural interventions for sleep problems in adults aged 60+. Cochrane Database Syst Rev, 2003(1): p. CD003161.
39. Chesson, A.L., Jr., et al., Practice parameters for the nonpharmacologic treatment of chronic insomnia. An American Academy of Sleep Medicine report. Standards of Practice Committee of the American Academy of Sleep Medicine. Sleep, 1999. 22(8): p. 1128-33.
40. Morin, C.M., et al., Psychological and behavioral treatment of insomnia:update of the recent evidence (1998-2004). Sleep, 2006. 29(11): p. 1398-414.
41. Berger, A.M., Update on the state of the science: sleep-wake disturbances in adult patients with cancer. Oncol Nurs Forum, 2009. 36(4): p. E165-77.
42. Santos, R.V., S. Tufik, and M.T. De Mello, Exercise, sleep and cytokines: is there a relation? Sleep Med Rev, 2007. 11(3): p. 231-9.
43. Chesson, A.L., Jr., et al., Practice parameters for the use of light therapy in the treatment of sleep disorders. Standards of Practice Committee, American Academy of Sleep Medicine. Sleep, 1999. 22(5): p. 641-60.
44. Bruera, E., et al., Rapid discontinuation of hypnotics in terminal cancer patients: a prospective study. Ann Oncol, 1996. 7(8): p. 855-6.
45. Bonnet, M.H., et al., The use of stimulants to modify performance during sleep loss: a review by the sleep deprivation and Stimulant Task Force of the American Academy of Sleep Medicine. Sleep, 2005. 28(9): p. 1163-87.
46. Brzezinski, A., et al., Effects of exogenous melatonin on sleep: a meta-analysis. Sleep Med Rev, 2005. 9(1): p. 41-50.
47. Simeit, R., R. Deck, and B. Conta-Marx, Sleep management training for cancer patients with insomnia. Support Care Cancer, 2004. 12(3): p. 176-83.
48. Andersen BL, Farrar WB, Golden-Kreutz DM, Glaser R, Emery CF, Crespin TR, Shapiro CL, Carson WE 3rd. Psychological, behavioral, and immune changes after a psychological intervention: a clinical trial. J Clin Oncol. 2004;22:3570–80.
49. Atanackovic D, Kro¨ger H, Serke S, Deter HC. Immune parameters in patients with anxiety or depression during psychotherapy. J Affect Disord. 2004;81:201–9.
50. Cooper NJ, Keage H, Hermens D, et al. The dose-dependent effect of methylphenidate on performance, cognition and psychophysiology. J Integr Neurosci. 2005 Mar;4(1):123-44.
51. Bruera E, Strasser F, Palmer JL, et al. Effect of fish oil on appetite and other symptoms in patients with advanced cancer and anorexia/cachexia: a double-blind, placebo-controlled study. J Clin Oncol. 2003;21:129-34.
52. Bruera E, El Osta B, Valero V, et al. Donepezil for cancer fatigue: a double-blind, randomized, placebo controlled trial. J Pain Symptom Manage. 2003 Nov;26(5):1049-54.
53. Richardson MA, Sanders T, Palmer JL, et al. Complementary/alternative medicine use in a comprehensive cancer center and the implications for oncology. J Clin Oncol. 2000 Jul;18(13):2505-14.
54. Martiny K, Lunde M, Unden M, Dam H, Bech P. The lack of sustained effect of bright light, after discontinuation, in non-seasonal major depression. Psychol Med. 2006;36(9):1247-1252.
55. Riemersma-van der Lek RF, Swaab DF, Twisk J, Hol EM, Hoogendijk WJ, Van Someren EJ. Effect of bright light and melatonin on cognitive and noncognitive function in elderly residents of group care facilities: A randomized controlled trial. JAMA. 2008;299(22):2642-2655.
56. Badr H, Carmack Taylor CL. Social constraints and spousal communication in lung cancer. Psycho-Oncology. 2006;15:673-683.

57. Badr H, Carmack Taylor CL. Effects of relationship maintenance on psychological distress and dyadic adjustment among couples coping with lung cancer. Health Psychology. 2008;27(5):616-627.
58. Badr H, Carmack Taylor CL. Effects of relationship talk on the psychological and marital adjustment of lung cancer patients and their partners. Journal of Cancer Survivorship. 2008;2(1):53-64.
59. Carmack Taylor CL, Gritz ER, Basen-Engquist K. Active for Life after cancer: A randomized trial examining a lifestyle physical activity program for prostate cancer patients. Psycho-oncology 2006;15:847-62.
60. Carmack Taylor CL, Smith MA, de Moor C, Dunn AL, Pettaway C, Sellin R, et al. Quality of life intervention for prostate cancer patients: design and baseline characteristics of the Active for Life after cancer trial. Controlled Clinical Trials 2004;25:265-85.
61. Carmack Taylor CL, de Moor C, Basen-Engquist K, Smith MA, Dunn AL, Badr H, et al. Moderator analyses of participants in the Active for Life after cancer trial: implications for physical activity group intervention studies. Ann Behav Med 2007;33(1):99-104.
62. Bruera E, Strasser F, Palmer JL, et al. Effect of fish oil on appetite and other symptoms in patients with advanced cancer and anorexia/cachexia: a double-blind, placebo-controlled study. J Clin Oncol. 2003;21:129-34.
63. Buysse DJ, Reynolds CF,3rd, Monk TH, Berman SR, Kupfer DJ. The pittsburgh sleep quality index: A new instrument for psychiatric practice and research. Psychiatry Res. 1989;28(2):193-213.
64. Buysse DJ, Ancoli-Israel S, Edinger JD, Lichstein KL, Morin CM. Recommendations for a standard research assessment of insomnia. Sleep. 2006;29(9):1155-1173.
65. Cella D. Manual of the Functional Assessment of Chronic illness Therapy (FACIT) Measurement System. Center on Outcomes, Research and Education (CORE), Evanston Northwestern Healthcare and Northwestern University. Version 4, 1997.
66. Johnston M, Pollard B, Hennessey P. Construct validation of the hospital anxiety and depression scale with clinical populations. J Psychosomatic Res. 2000; 48:579-584.
67. Bruera E, Kuehn N, Miller MJ, Selmser P, Macmillan K. The Edmonton Symptom Assessment System(ESAS): a simple method for the assessment of palliative care patients. J Palliat Care. 1991;7:6-9.
68. Gibbins J, McCoubrie R, Kendrick AH, Senior-Smith G, Davies AN, Hanks GW. Sleep-wake disturbances in patients with advanced cancer and their family carers. J Pain Symptom Manage. 2009.
69. Tonetti L, Pasquini F, Fabbri M, Belluzzi M, Natale V. Comparison of two different actigraphs with polysomnography in healthy young subjects. Chronobiol Int. 2008;25(1):145-153.
70. Reuben, J.M., Lee, B.-N., Johnson, H., et al. Restoration of Th1 cytokine synthesis by T cells of patients with chronic myelogenous leukemia in cytogenetic and hematologic remission with interferon-α. Clin Cancer Res. 2000; 6: 1671-7.
71. Morin CM; Belleville G; Bélanger L; Ivers H. The insomnia severity index: psychometric indicators to detect insomnia cases and evaluate treatment response. *SLEEP* 2011;34(5):601-608.
72. Bastien CH, Vallières A, Morin CM. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. Sleep Med. 2001;2(4):297–307, pmid:11438246.

73. Breitbart W, Rosenfeld B, Roth A, Smith MJ, Cohen K, Passik S. The memorial delirium assessment scale. *Journal of Pain and Symptom Management.* 1997;13(3):128-137.
74. Grassi L, Caraceni A, Beltrami E, et al. Assessing Delirium in Cancer Patients. The Italian Versions of the Delirium Rating Scale and the Memorial Delirium Assessment Scale. *Journal of Pain and Symptom Management.* 2001;21(1):59-68.