The following protocol information is provided solely to describe how the authors conducted the research underlying the published report associated with the following article:

Methylphenidate and/or a Nursing Telephone Intervention for Fatigue in Patients with Advanced Cancer: A Randomized Placebo-Controlled Phase II Trial

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Objectives

1) Determine if methylphenidate 5 mg taken as needed is superior to placebo in the treatment of **fatigue in advanced cancer patients** as measured by the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) subscale.
2) Secondary objective-1: Determine if a nursing telephone intervention (NTI) improves fatigue (measured by the FACIT-F subscale) as compared to standard care in patients receiving methylphenidate and placebo.
3) Secondary objective-2: Investigate the additive or synergistic effect of methylphenidate treatment plus NTI reduction of fatigue compared to either methylphenidate treatment or NTI alone.
4) Secondary objective-3: To investigate the additive or synergistic effect of Methylphenidate treatment plus Nursing Telephone Intervention (NTI) in the reduction of other associated symptoms such as depression, sleep, anxiety, and health related quality of life.

1.0 Grant Information

The NIH grant for this protocol is # NIH R01 NR010162-01A1.

3.0 Background

Fatigue is a Major Problem in Cancer Patients. Fatigue is reported by 60-90% of patients with advanced cancer as their most frequent and debilitating symptom [1-2]. Cancer related fatigue is defined as "an unusual, persistent, subjective sense of tiredness related to cancer or cancer treatment that interferes with usual functioning" [2]. Fatigue consists of three major components: easy tiring and reduced capacity to maintain performance; generalized weakness (i.e., the anticipatory sensation of difficulty in initiating a certain activity); and mental fatigue, defined as the presence of impaired mental concentration, loss of memory, and emotional lability.

Fatigue can interfere with a patient's ability to perform physical and social activities [3]. It may also affect a patient's decision-making regarding future treatment, leading to refusal of potentially curative or supportive treatment. In the majority of patients with advanced cancer, the etiology of fatigue is unclear but the effect is similar. Fatigue is difficult on the patient and the family. Fatigue interferes with activities of daily living (e.g., grooming, meal preparation) and robs patients of time and energy to engage in routine activities with there loved ones. This greatly decreases a patient's quality of life. In most patients with advanced cancer, fatigue is a multi-causal syndrome due to a number of physical and psychosocial mechanisms [4, 5]. Cancer produces tumor by-products or induces immune cytokines capable of producing fatigue directly or indirectly by causing cachexia, muscle loss or deconditioning [6-7]. These mechanisms, in addition to medications to treat these conditions (i.e., opioid and other drugs), are capable of causing neurocognitive changes and hypogonadism [8-10]. Also, cancer patients frequently develop depression and anxiety [4-7]. Fatigue is a major component of somatization in patients with mood changes and it has been found to strongly correlate with depression and anxiety. Chemotherapy and radiation therapy can cause fatigue both directly and indirectly through the production of anemia [6].

In patients with advanced cancer, fatigue is almost universal and severe even when hemoglobin is appropriately corrected and anemia is treated with erythropoietin or darbopoietin [4, 5] Most patients with advanced cancer have fatigue before receiving any treatment and fatigue persists after the discontinuation of chemotherapy and radiation, strongly suggesting that many of the other causative factors continue to have an impact on the brain's perception of fatigue. All of the available data suggest that despite the various mechanisms that have been identified as causing fatigue, one common denominator is that they all act on the brain to cause the subjective symptom of fatigue. Thus, it is logical that an agent such as methylphenidate, with demonstrated central-stimulating activity, may reduce the severity of fatigue.

Current Treatments for Cancer- Related Fatigue. Most patients with advanced cancer do not receive specific treatment for fatigue [4,7]. Patients frequently under report fatigue as a symptom because of reluctance to distract providers from treatment of their tumor or other severe symptoms (e.g. pain). In addition, because of the difficulty in treating fatigue, health care professionals may be reluctant to discuss it [6]. When patients report fatigue, physicians usually look for a number of reversible causes such as

anemia, depression or anxiety, medications, or metabolic abnormalities [4-7]. Unfortunately, even when these abnormalities are identified and corrected, patients usually continue to report high levels of fatigue [5,6]. Our group and others have conducted randomized controlled trials of corticosteroids for the treatment of fatigue [11,12]. These drugs appear to have significant but transient effects (usually less than 3-4 weeks) and are associated with adrenal suppression and major potential side effects, including infections, myopathy, osteoporosis, or Cushing syndrome. Other pharmacological treatments of fatigue (e.g., testosterone and donepezil) have also been evaluated in preliminary investigations [13-16]. While testosterone replacement in patients experiencing hypogonadism may prove to be an effective treatment of fatigue [14], the effects of testosterone replacement in women are not understood and the side effects in men are still being debated and examined [17,18]. Although Donepezil has been found to alleviate fatigue-related symptoms, this treatment can cause severe gastrointestinal side effects [13]. Thus, there is great need for effective symptomatic treatments for fatigue. The National Comprehensive Cancer Network has established guidelines for the screening, evaluation, and intervention of cancer related fatigue [2]. These guidelines recommend the investigation of psychostimulants as a pharmacological therapy for cancer related fatigue. Methylphenidate is a psychostimulant that has the potential to treat cancer-related fatigue.

Methylphenidate and Fatigue. Methylphenidate is a central nervous system (CNS) stimulant, and its mechanism of action is blockage of presynaptic dopamine re-uptake [19]. It presumably activates the brain stem arousal system and cortex to produce its stimulant effect. Methylphenidate has a rapid onset of action, with peak plasma concentrations in one to three hours and a plasma half-life of 1.5 to 2.5 hours (concentrations in the brain exceed those in plasma). The peak effect is at 2 hours, with duration of action of 3 to 6 hours. Methylphenidate is usually administered twice a day, at breakfast and at lunch, in order to minimize insomnia. However, due to its rapid onset of action and short half-life, methylphenidate may be effective in relieving fatigue when taken on an as needed basis throughout the day. This flexible administration regimen may significantly improve patient quality of life. Methylphenidate is more frequently used for the management of attention deficit and hyperactivity disorder [20] and for depression, particularly in geriatric patients [21]. In patients with cancer, methylphenidate has been used successfully to manage opioid-induced sedation [22,23], cognitive failure associated with brain tumors [24], and depression [21, 25].

Preliminary reports have suggested success with psycho-stimulants in treating fatigue in cancer patients as well as patients with other chronic illnesses [26-28]. Methylphenidate has been found to improve fatigue in ambulatory patients with human immunodeficiency virus [28]. In the palliative care setting, methylphenidate has been used in the management of opioid-induced sedation and depression [22, 25, 31]. Sarhill and colleagues reported a rapid reduction of fatigue in 9 of 11 consecutively treated patients in an open-label study [29]. A pilot study of 14 evaluable patients with advanced cancer found that methylphenidate at a dose of 5-10 mg/day significantly improved fatigue after 7 days [30].

The side effects of methylphenidate are usually mild and generally well tolerated. Nervousness and insomnia are the most common adverse reactions but are usually controlled by reducing dosage and omitting the drug in the afternoon or evening. Other reactions include hypersensitivity (including skin rash, urticaria, fever, arthralgia, exfoliative dermatitis, and erythema multiforme), anorexia, nausea, dizziness, palpitations, headache, drowsiness, and change of blood pressure, tachycardia, angina, cardiac arrhythmia, and abdominal pain. There have been rare reports of Tourette's syndrome.

Methylphenidate can be transformed from a therapeutic agent to an abused and addictive substance when this drug is taken in excessive amounts and used through intranasal and intravenous routes. Methylphenidate abuse produces psychiatric side effects similar to those of cocaine and amphetamines, such as nervousness, restlessness, agitation, suspiciousness, paranoia, hallucinations and delusions [32]. The potential for methylphenidate abuse has been addressed primarily through regulatory measures. These include adding a higher level of surveillance by assigning it to schedule II status. Other measures to reduce methylphenidate abuse include assessment of history of drug and substance abuse, tablet counts, and education about the abuse potential.

Fatigue-Related Outcomes. We know from the literature that methylphenidate has been found to reduce outcomes (e.g., depression, insomnia, physical activity) associated with fatigue. In particular, methylphenidate has been reported to be an effective treatment for depression [21,25,31]. In a study of 30

depressed cancer patients, researchers found one-third demonstrated marked improvement and almost half (n =13) demonstrated moderate improvement when treated with methylphenidate [31]. In another study of 30 cancer patients, Homsi and investigators [25], found that 21 of the patients studied reported that they were not depressed after only three days of treatment. They also found that methylphenidate effectively and rapidly improved symptoms of depression in 10 advanced cancer patients [33].

In another randomized, controlled trial, methylphenidate given to 32 adults with attention-deficit disorder also demonstrated improvements in depression, anxiety and irritability [34]. These findings suggest that methylphenidate will improve the mood of advanced cancer patients. Though studies of cancer patients have observed improvements in depression after treatment with methylphenidate, many of these studies have had very small sample sizes. Also, these studies have not been controlled, making it impossible to eliminate a placebo effect as an explanation for the findings. However, studies with other patient populations have found that methylphenidate can be an effective treatment for depression.

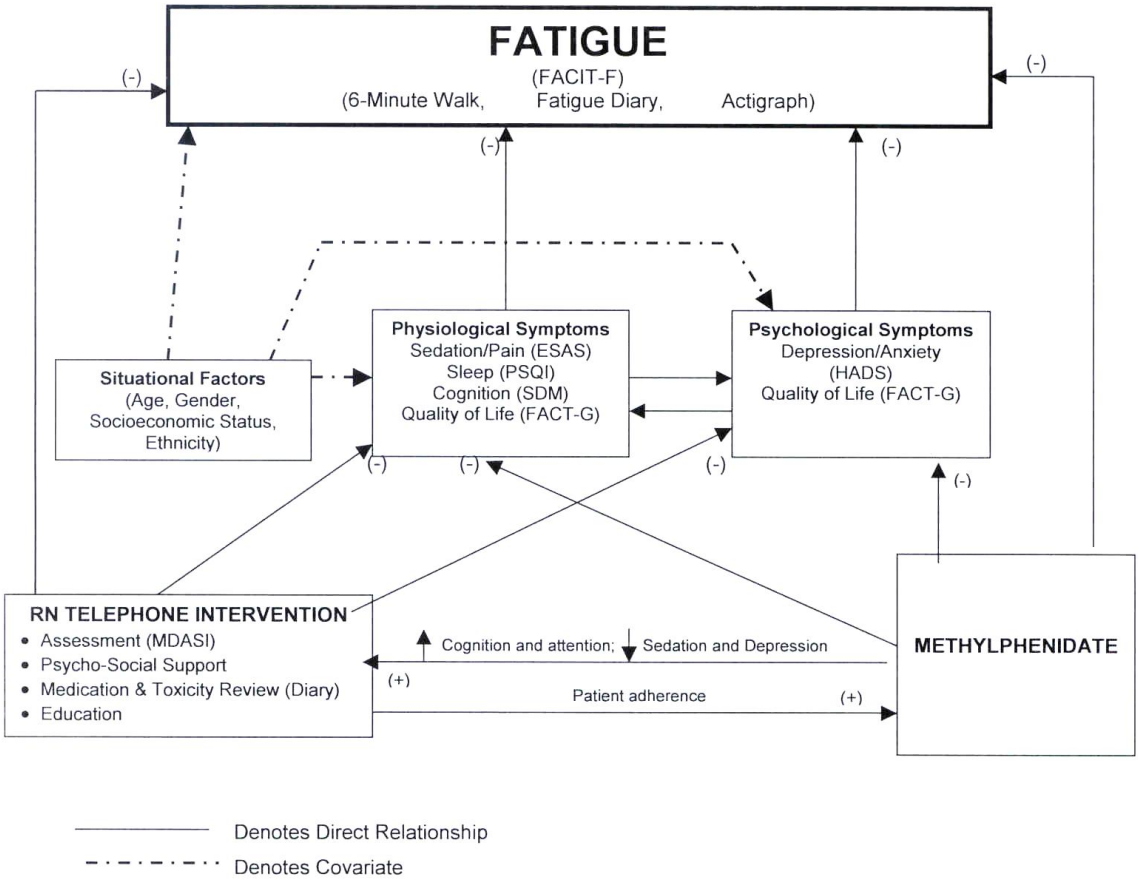
Sleep disturbance and insomnia, a frequent problem in patients with advanced cancer, are associated with fatigue. While insomnia has been reported as a potential side effect of methylphenidate [35], some reports have indicated that methylphenidate can reduce insomnia, particularly in adults [36-38]. In a double-blind crossover study of the effects of late-afternoon administration of methylphenidate in children with attention-deficit hyperactivity disorder, researchers did not find adverse effects on sleep latency when a third dose of methyl-phenidate was administered in the late afternoon (4 pm) [36]. In a double blind, placebo-controlled six-week crossover study of 35 adults with traumatic brain injury, insomnia was not significantly related to methylphenidate [37]. Further, in our previous research we found that patient's sleeping patterns were improved while taking methylphenidate [38]. We believe that methylphenidate may improve insomnia by reducing fatigue, lethargy, and depression symptoms and probably by also reducing daytime napping. This may lead to patients getting more adequate sleep at nighttime.

As we have observed that methylphenidate improves activity [22], we hypothesize that patients with less fatigue and improved mood will increase their level of activity. We expect that they will more frequently be able to perform their activities of daily living (such as self hygiene, food preparation, socialization, etc.) and they may even be able to spend more time outside their home. Mini-Motionlogger™ Actigraph will be used to measure physical activity. This device is worn on the wrist and unobtrusively monitors motion. The actigraph can be used to record and evaluate sleep quantity and quality, daytime activity levels, and napping. Actigraphy is considered a useful method for measuring daily physical activity [39]. However, findings from some researchers suggest that changes in fatigue cannot be assumed to automatically correspond with an accompanying change in physical activity. However, other findings indicate that physical activity may correspond with fatigue in ill patients. While Dimsdale and colleagues found no correlation between fatigue expression and actigraph measurements in healthy controls [40], Roscoe found that actigraph measurements significantly correlated with fatigue in patients with breast cancer [41].

Impact of Nurse Telephone Interventions on Fatigue and Other Symptoms. In our studies, patients have responded favorably to nursing telephone interventions (NTI) in addition to methylphenidate treatment. Research has demonstrated that patients and their families' welcome nurse telephone interventions, as a way of maintaining contact with healthcare professionals [42]. However, there is much debate regarding the effectiveness of these interventions on clinical outcomes. One study found that nursing telephone interventions are able to augment the treatment of depression in primary care [43]. In this study, 302 patients with depression were randomized to usual physician care (123 patients), nurse tele-health care consisting of 12-14 calls of approximately 10 minutes each over 16 weeks (117 patient), and combined nurse telehealth plus a peer support group (62 patients). At 6 weeks and 6 months the nurse tele-health group had a significantly higher rate of improvement in the Hamilton Depression Rating Scale, Beck Depression Inventory, and treatment satisfaction score than the usual physician care group. At week 6, the nursing telehealth group also had significantly higher improvement in the SF-12 mental functioning scale score than the usual physician care group [43]. The investigators did not find that adding peer support to the telehealth group further improved outcomes. Other studies have found that nurse-led interventions for patients with ovarian cancer were perceived by patients as being helpful in regards to symptom management, assessment of side effects, and promotion of self care [44]. Ponica found that next day follow up calls in elderly patients after discharge resulted in a significant number of interventions in the form of advice or action to ensure

patients well being [45]. Other findings regarding nurse phone interventions suggest that nursing interventions reduce unscheduled hospital visits [46-47]. For example, one study found that patients receiving pelvic radiotherapy and nurse-led follow up were able to reduce the number of emergency clinic visits [46]. In contrast, telephone support in the early post-discharge period following elective cardiac surgery was not able to reduce anxiety and depression levels [47] calling into question the efficacy and generalizability of nursing phone interventions. A growing body of literature has explored integrating qualitative components in intervention research. In a study that has similar features to what we are proposing in the qualitative component [48-50] tape recorded interventions were analyzed. The qualitative data from the nursing intervention, designed to reduce pain, added insights into why the intervention was not effective for a subset of patients, and other aspects of the intervention that were helpful and not helpful were made more clear so that the intervention could be improved in future research and clinical applications. This evidence as well as information we have obtained while conducting symptom management research leads us to believe that nurse phone calls may have a positive impact on patient's symptom reduction and quality of life.

Theoretical Model: Figure 1. Model for the effects of methylphenidate and NTI for cancer related fatigue



The model [Figure 1] guiding the research we are proposing is an adaptation and modification of the Middle-Range Theory of Unpleasant Symptoms [51]. This theory describes the effects and interactions of symptom production. Methylphenidate, which will decrease sedation, improve cognition, and reduce pain, and the nursing telephone intervention (NTI), which will improve adherence to medications, such as analgesics, antiemetic, etc., both can influence physiological factors affecting fatigue. Methylphenidate (improving depression) and NTI (providing educational and emotional support) can also influence psychological factors. Finally, covariates such as age, gender, socio-economic status and ethnicity can be interpreted as situational

factors. As described by Lenz et al, there is considerable interaction among different physiological, psychological, and situational influences on cancer fatigue. In addition, both interventions can influence each other: the NTI can enhance the effects of methylphenidate by improving adherence, and methylphenidate can enhance the effects of NTI by reducing sedation and depression and by improving cognition and attention. Both methylphenidate and the NTI will improve quality of life (FACT-G) by reducing fatigue, physiological symptoms, and psychological symptoms. We will include the effect of covariates (situational factors) such as age, gender, socio-economic status, and ethnicity in all analyses.

In the final analysis, we will need to determine; does the number of phone calls influence the response to NTI? We will include the number of phone calls received, as a co-variate in analyses to adjust for possible effects on response. In addition, if the number of phone calls received is a significant effect, we will further report and analyze the number of phone calls received in relationship to outcome responses to NTI.

Summary. Our previous research has indicated that methylphenidate can reduce fatigue, fatigue-related outcomes, and improve quality of life in advanced cancer patients. Since we have found improvements in psychosocial outcomes in medication treatment studies that included a nurse phone call even in the placebo group, we expect that the nursing telephone interventions will interact with the treatment effects of methylphenidate to improve fatigue-related outcomes and overall quality of life above methylphenidate treatment alone. As the synergistic effect between nursing telephone interventions and methylphenidate has not been evaluated in a randomized-controlled trial, we have no empirical information on this relationship. Our study will fill this gap and provide valuable information on the ability of nursing telephone interventions to enhance medication treatment effects and the effect of methylphenidate alone on fatigue-related outcomes.

Significance. Interventions that alleviate multiple sources of fatigue and fatigue-related symptoms are greatly needed in the clinical setting to treat the multiple fatigue-related symptoms experienced by advanced cancer patients. Improving fatigue and treating fatigue-related symptoms will greatly improve the quality of life of advanced cancer patients. Additionally, the interaction between methylphenidate and nurse telephone follow-up on cancer-related fatigue has not been studied. Nurse telephone follow-up has the potential to reduce emergency visits and increase a patient's adaptive coping responses to illness. Combining nurse telephone follow-up with a pharmacological treatment may provide more effective management of symptoms experienced by patients at the end of life. Thus, this treatment has the potential to help the patients better manage their symptoms, which improves their quality of life, and this treatment can be easily implemented in clinical practice. If found effective, these two interventions will result in immediate changes in standard of care, as there is not yet an established, standard treatment for cancer-related fatigue.

PRELIMINARY STUDIES

Pharmacological Treatment of Fatigue. The PI's initial studies in symptom management in advanced cancer patients allowed us to establish the high frequency of fatigue in different patient populations [52-57]. We conducted studies on different assessment methods for fatigue [55] and started the process of characterizing the association between fatigue and other complications of advanced cancer, including cachexia [52, 56-57] and hypogonadism [9-10]. These studies helped us better understand fatigue as a frequent, severe, and multi-causal syndrome.

Initially, we evaluated the effects of corticosteroids on alleviating fatigue in cancer patients. In a randomized placebo-controlled study of 31 patients, we found that methylprednisolone improved subjective fatigue, pain, and appetite as compared to placebo in patients with advanced cancer [54]. However, the effects lasted less than 3 weeks and, as described earlier, corticosteroids had a variety of severe side effects. In later studies on the treatment of cancer cachexia, we observed mild improvement in fatigue in patients receiving megestrol acetate [11, 52] and polyunsaturated fatty acids [58] as compared to placebo. However, these drugs were found to have limited efficacy for cancer cachexia and fatigue. In a pilot study of Donepezil, a long-acting selective acetylcholinesterase inhibitor, 27 patients were provided 5 mg of this medication for 7 days to counteract opioid-induced sedation, we found a significant decrease in sedation and fatigue with this medication [13]. Seven patients had discontinued the study by day 7. While two patients discontinued the study because of difficulties unrelated to the study drug, 5 patients experienced side effects

that may have been attributable to the study drug, with mild to moderate nausea being the most common reason for study discontinuation. In the 20 remaining study patients, the FACIT-F (measure of subjective fatigue) scores of improved from 17.8 ± 9.9 to 27.2 ± 13.1 at day 7 (p = 0.0004). Although these findings indicated that these drugs (corticosteroids or Donepezil) were not the most effective treatment for cancer-related fatigue due to their side effects, they helped us further refine our methodology for pharmacological trials for treating fatigue.

In conducting treatment studies of the efficacy of methylphenidate in decreasing opioid-induced sedation [22], we discovered that methylphenidate also decreases drowsiness and increases activity, leading us to believe that it might be an effective treatment for fatigue in cancer patients. In a three-day trial of 32 patients with cancer-related pain, we randomized patients to a group receiving 10 mg of methylphenidate with breakfast and 5mg with lunch or a group receiving placebo. Patients received methylphenidate or placebo for 3 days and during day 4 a cross-over took place. As can be seen in Table 1, there was a significant improvement in drowsiness, subjective activity and pain during the methylphenidate phase as compared to placebo [22]. In addition, there was no significant change in anxiety or hours of sleep.

TABLE 1. Results after the completion of the double-blind study in 28 evaluable patients*

Feature	Baseline (B)†	P value (B vs P)	Placebo (P)†	P value (P vs MP)	Methylphenidate (MP)†
Pain intensity - Days 0,3,and 6 at 10:00am (VA 0-100)	64±31	P < 0.01	55 ± 24	P < 0.01	43 ± 27
Pain intensity - Daily at 8:00am (VA 0-100)	70 ± 30	P < 0.05	59 ± 28	P < 0.01	40 ± 28
Activity (VA 0-100)	31 ± 29	P < 0.15	41 ± 26	P < 0.05	57 ± 25
Drowsiness (VA 0-100)	36 ± 21	P = 0.10	45 ± 27	P < 0.01	58 ± 24
Depression (VA 0-100)	59 ± 31	NS	64 ± 28	NS	69 ± 25
Anxiety (VA 0-100)	58 ± 28	NS	60 ± 27	NS	65 ± 25
Hours of sleep	6.5 ± 2	NS	6.3 ± 2	NS	6.5 ± 2

* VA = visual analogue; NS = not significant

† Values are expressed as mean ± SD

In an open study of 50 patients with opioid-induced sedation, we found that methylphenidate 50mg/day improved sedation in 48 patients [53]. Although fatigue was not specifically measured in this study, patients anecdotally reported a reduction a fatigue. In these studies there appeared to be an improvement in fatigue with methylphenidate as compared to placebo when measured as an ancillary outcome. However, in a follow-up study on the neuropsychological effects of methylphenidate in patients receiving parenteral opioids, we did not observe an improvement in fatigue as compared to placebo [23]. However, in this study, fatigue was only measured at one time point, two hours after receiving methylphenidate. Our findings after multiple clinical trials and frequent clinical use of methylphenidate in patients with advanced cancer suggested that it was safe and effective for the management of opioid-induced sedation but it also appeared to have effects on fatigue and other fatigue-related outcomes. However, our studies on the management of opioid-induced sedation did not allow us to appropriately characterize the effects of methylphenidate on fatigue and fatigue-related symptoms, as this study sample only included advanced cancer patients suffering from opioid induced sedation.

Based on our preliminary observations, Breitbart and colleagues conducted a randomized controlled trial of methylphenidate 7.5 mg twice daily, pemoline 18.75 mg twice daily, or placebo capsule twice daily for the management of fatigue in 144 patients with AIDS [28]. Methylphenidate and pemoline were both superior to placebo. These findings, in addition to our clinical observations of improvement in multiple symptoms in patients treated with methylphenidate for sedation, led us to design a pilot study of methylphenidate for the treatment of cancer fatigue.

We hypothesized that a treatment regimen allowing patients to titrate the administration schedule of methylphenidate to their level of fatigue and expected level of activity might be more efficacious than a fixed schedule regimen [37]. We postulated that given the rapid onset of action of methylphenidate and its short half-life, it might be possible to use 5 mg capsules on an as needed basis. Thus, 31 participants with advanced cancer and fatigue who rated their fatigue as ≥ to 4 on a 0-10 rating scale were prescribed methylphenidate 5 mg capsules as needed every 2 hours for patient-described fatigue. Patients were allowed to take a maximum of 4 capsules per day. Patients received a daily nurse phone call for symptom assessment and support. 30/31 patients were evaluable by day 7. Results from the first seven days of this study are summarized below in Table 2. Overall, 28 of 30 patients (93%) had improved fatigue (defined as a decrease of more than 2 on a 0-10 scale) by Day 7.

After the assessment at Day 7, all 30 patients (100%) chose to continue treatment with methylphenidate. Twenty-eight patients (93%) took 3 or more methylphenidate capsules daily, and all 30 patients took an afternoon or evening dose. The findings remained stable in 21 patients who remained evaluable at Day 28.

Methylphenidate was very well tolerated in these patients with advanced cancer and no patient required discontinuation due to side effects. Two patients reported increased restlessness; 1 patient reported increased dizziness, 2 patients reported increased anorexia; 1 patient reported a 2-day self resolved skin rash; 1 patient reported intermittent vertigo for 2 days; and 1 patient reported self-resolved tachycardia for 3 days. In all cases, symptoms were mild and did not require treatment.

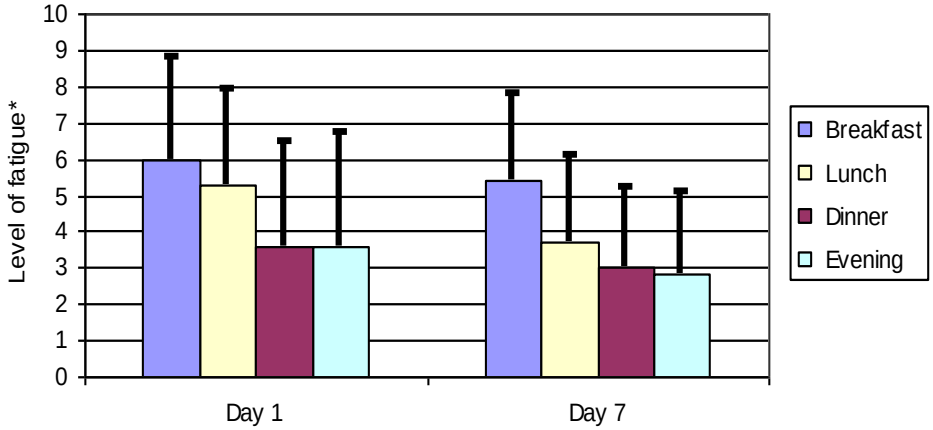
Table 2. Comparison of Mean ESAS * FACT-G, FACIT-F at Baseline and Day 7 (n=30) and day 28 (n =21)

Variable	Symptom-Assessment Score (SD)					
	Baseline (n=30)	Day 7 (n=30)	P value**	Baseline (n=21)	Day28 (n=21)	P value****
ESAS*						
Fatigue	7.2 (1.6)	3.0 (1.8)	<.001	7.1 (1.5)	3.1 (2.6)	<0.001
Pain	5.0 (2.4)	3.8 (1.8)	.005	4.6 (2.6)	3.9 (2.8)	0.34
Depression	3.6 (2.9)	1.1 (1.5)	<.001§	2.9 (2.9)	1.7 (2.3)	0.17
Anxiety	3.5 (3.1)	1.3 (1.5)	.002§	2.7 (3.0)	1.7 (2.2)	0.14ǂ
Appetite	4.5 (3.1)	2.4 (2.0)	<.001	4.1 (3.1)	2.8 (3.2)	0.007†
Sleep pattern	5.3 (2.4)	2.2 (1.8)	<.001§	5.2 (2.5)	3.3 (3.0)	0.005
FACT-G***						
Total sub score	65.7 (17.1)	81.4 (14.7)	<.001	68.1 (16.8)	79.4 (19)	0.03
FACIT-F***						
Fatigue sub score	17.5 (11.3)	34.7 (10.0)	<.001	18.4 (9.5)	38.4 (14)	<0.001

Abbreviations:
ESAS Edmonton Symptom Assessment Scale;
FACIT-F Functional Assessment for Chronic Illness Therapy- Fatigue
*Score: 0 = best; 10 = worst possible.
**Comparisons were made between baseline and day 7, using a paired *t* test if the data were normally distributed and a sign test otherwise (noted by §). Since many statistical tests were made, we consider that statistical significance has been shown by *p*-value ≤ .005 instead of the usual value of .05.
*** Higher scores indicate better functioning.
**** Comparisons were made between baseline and day 28, using a paired *t* test if the data were normally distributed and a sign test otherwise (noted by ǂ).

In this study [38], patients maintained a daily diary in which they were required to record their fatigue, as one of the endpoints for this study, at breakfast, lunch, dinner and before bedtime. We found that fatigue varied considerably during the course of the day, bolstering our belief that administering methylphenidate on "as needed basis" is the most effective treatment for fatigue in advanced cancer patients. In ratings recording at baseline and at day seven, we found that fatigue progressively decreased from morning to evening. We found significant differences in the amount of fatigue reported based on the time of day at day 1 (p = 0.0023) and day 7 (p = 0.0008). This is illustrated in Figure 2.

Figure 2. Fatigue intensity according to time of the



Our results indicate that methylphenidate is very well tolerated in the advanced cancer population [38]. In addition, our findings suggested that this drug is able to improve fatigue and a number of other symptoms, including the overall score, on our measure of quality of life (FACT-G) and the subscale score on a measure of fatigue (FACIT-F). However, our pilot study had a number of limitations. Fatigue is a subjective symptom and as such can only be appropriately tested in double blind trials. As this was an open-label study, we could not rule out the possibility of a strong placebo effect. As we found that several symptoms (i.e., depression, anxiety, insomnia, and pain) in addition to fatigue, improved, suggesting that the results might be partly attributable to placebo or to a response to the daily nurse phone calls. However, the robust response for an observation period of 1 week followed by 4 weeks of treatment with maintained overall symptom improvement and satisfaction suggested that these results were genuine symptomatic effects. Our study was also unable to establish whether methylphenidate effected fatigue directly or indirectly by influencing other symptoms such as depression, drowsiness, or anxiety**.**

Nursing Telephone Interventions (NTI). As illustrated in Table 2, we observed major clinical and statistically significant improvement in a large number of physical and psychosocial symptoms in our pilot study of methylphenidate [38]. This improvement was unexpected in the case of some symptoms such as insomnia, appetite, or anxiety, leading us to wonder if some of the effects that we noted were attributable to some factor other than the methylphenidate. Considering that patients frequently expressed appreciation for the daily nursing telephone interventions, we speculated that the nursing telephone interventions might be another factor impacting patient symptom improvement. We observed a similar expression of satisfaction with nursing telephone interventions in a previous pilot study of Donepezil [13] where we also observed significant improvement in a number of symptom variables, and previous studies on polyunsaturated fatty acids [58] and megestrol acetate [52] also provided evidence of patient satisfaction with the nursing telephone interventions. We also hypothesize that dramatic improvement in fatigue in both methylphenidate and placebo groups in our pilot randomized trial can be explained at least partially by the effects of the daily nursing telephone interventions. In the process of conducting our clinical trials, we have developed expertise in conducting nursing telephone interventions.

We recently completed a pilot randomized, double-blind controlled trial comparing patient controlled methylphenidate (PCM) versus placebo for cancer fatigue. 105 patients were randomized to receive PCM 5 mg every 2 hours as needed for 7 days [maximum 20 mg/day] [n=52] or placebo [n=53]. All patients received a daily nursing telephone intervention (NTI). The difference between baseline and day 8 are shown in table 3. Fatigue and other symptoms improved dramatically by day 8 in both the PCM and placebo group (a mean improvement in FACIT-F fatigue subscale was 9.6 and 7.5 points, respectively). There was a trend favoring PCM over placebo, but it was not significantly different. In this study, we did not ask what patients believed they were taking but we asked how beneficial they found the drug at the end of the 7-day double-blind period.

14/53 patients expressed a considerable and consistent benefit from placebo (26%). We believe that these results can be explained by the fact that the nursing telephone intervention had such major impact on fatigue, and also because the duration of the study was only one week, thereby not allowing for enough time to observe a clear cut difference between methylphenidate and placebo effects. Our proposed study will address these two issues by comparing PCM vs. placebo in a group not receiving nursing telephone intervention, and by extending the double blind phase of the study to two weeks.

Table 3. Mean difference symptom intensity between baseline and day 8.

Symptom	PCM + NTI (Day 8-baseline)	Placebo + NTI (Day 8-baseline)	P-value
FACIT-F	**9.6 (± 9.8)**	**7.5 (± 11.3)**	**0.31**
FATIGUE	**-2.7 (±2.6)**	**-1.9 (± 2.8)**	**0.14**
PAIN	**-1.1 (±3.0)**	**1.1 (±2.9)**	**0.95**
DEPRESSION	**-1.4 (±2.6)**	**-1.3 (±2.9)**	**0.77**
DROWSINESS	**-1.4 (±2.9)**	**-1.1 (±2.9)**	**0.61**
SHORT OF BREATH	**-1.3 (±2.2)**	**-0.4 (±3.1)**	**0.08**
SLEEP	**-0.9 (±3.1)**	**-0.9 (±2.9)**	**0.95**
WELLBEING	**-1.7 (±2.7)**	**-0.7 (±3.2)**	**0.07**

FACIT-F: Positive value denotes improvement; other symptoms: negative value denotes improvement

To better understand the NTI, Dr. Marlene Cohen has joined the research team. Dr. Cohen's primary appointment is at the University Of Texas Houston School Of Nursing. She also is a Professor at MD Anderson in the Department of Symptom Research and is a nurse researcher at LBJ Hospital, part of the Harris County Hospital District. She has been investigating individuals' emotional responses to physical illness since 1981 and, specifically, among persons with cancer since 1990. Cohen's early work found that practitioners' and family members' understanding of patients' experiences differed from patients' views in important ways. Nurses focused their care on immediate problems and were preoccupied with their own approach (e.g., the best method to use to teach a patient about medication). In contrast, patients were concerned about the outcomes of the hospitalization and how their lives would change after hospitalization (59-64).

A study comparing cancer patients' and nurses' assessment of pain and pain relief (65) found that continued work is needed to ensure that pain is accurately assessed and relieved. A variety of nurse and patient characteristics altered the congruence of nurse assessment with patient self-assessment. The finding that pain management training in the nurses improved this congruence raises the potential for interventions to sensitize nurses to patient issues. Another aspect of this study was inclusion of an ethnically diverse group of patients with cancer. This study demonstrated the importance and feasibility of including an ethnically diverse sample. Pain ratings differed for African American and Hispanic patients but the differences were not statistically significant. However, this study had a small sample size with limited power to detect significant differences indicating the need for further research (65).

Another study of pain assessment found that despite the JCAHO standards for pain assessment, many areas of this assessment were not documented (66). An additional study conducted with nurses and physicians in the Department of Palliative Care & Rehabilitation Medicine illustrated the complexity of symptom assessment and expression. Phenomenological interviews with persons who reported low levels of pain but many other symptoms that were relieved with pain medications revealed patterns of experiences that helped to explain why persons might not report pain (67).

In a study with BMT patients, these patients discussed their learning needs in phenomenological interviews. Patients described a range of information needs, ranging from minimal to comprehensive and emphasized that information provided should be tailored to suit individual patient and family needs. For example, some patients felt that staff members would tell them what they needed to know, so they had no questions. Others wanted to know as much as possible about what to expect. These patients often went to

great lengths to obtain information, including searching the internet, contacting the National Cancer Institute, and searching in medical libraries. There was also a group between these two extremes of patients who had some questions and fears and who were not always clear about what to ask, how to ask it, or what might provide the information or reassurance they wanted (68). This finding led the clinicians involved to revise their interventions to address learning needs, which show that such data can yield information needed to develop and modify effective interventions.

A current study involves obtaining both phenomenological descriptions and symptom measures from patients at eight times over the first 100 days of their experience having blood and marrow transplantation (BMT). These data are currently being analyzed, but indicate that symptom reports from measures and those obtained in the phenomenological interviews can be usefully compared and that the data augment each other and add to our understanding of symptoms and effective interventions (69-70).
Cohen has also been involved in two studies of African American women (71-72), both of which involved interviewing African American women about their experiences with breast cancer screening. Her current study with BMT patients included African American and Latino patients, and the majority of the Latino interviews were conducted in Spanish, transcribed and translated and then analyzed. These studies demonstrated the ability to recruit African Americans and Latinos in research, and illustrate the willingness of Latinos and African Americans to participate in research that involves interviews.

In summary, since patients vary in their ability to express their needs, and since professionals do not as a whole understand patients' views, those who are alerted to potential needs will be quicker to respond to the earliest cues. Patients described professionals who sometimes responded in unhelpful ways; those who were aware of the patients' perspective may be less likely to ignore important concerns or to respond in inappropriate ways. Knowledge of these patterns of needs will provide a more effective base for clinical interactions and decision making. Cohen's prior research has shown that people are willing and able to describe their symptoms and health care experiences and that they can articulate the meaning of these experiences. Subjects IN These studies have included African Americans and Latinos. In addition, interventions have been suggested by these descriptions, and we expect in this study they will help us better understand the important aspects of the interventions being tested. Descriptions obtained from Cohen's prior research have also been useful to health care professionals who have not had the experiences being described. The "insider" experiences yield insights that provide a fuller understanding of the experiences, and our expectation is that the information obtained from analyzing the telephone interventions will add new, more detailed, understanding of the important aspects of fatigue and this intervention.

Other Fatigue-Related Outcomes. In conducting research on methylphenidate, we have found that it impacts other fatigue-related outcomes, particularly depression, activity, insomnia, and neurocognitive motor functioning. Our pilot study suggested that methylphenidate had clinical effects on both fatigue and depression [38], as illustrated in Table 2. In one randomized, double-blind placebo-controlled trial, Breitbart and colleagues, in a study of 144 ambulatory HIV patients found that in addition to improvements in fatigue (their primary outcome), significant associations were found between improvements in fatigue and improvements in depression [28].

As mentioned earlier, we found that methylphenidate improved activity levels in cancer patients receiving narcotics for the treatment of pain. In our most recent pilot study, patients also demonstrated a significant improvement in sleep patterns at day 7 (see Table 1) and day 28 after taking methylphenidate. At day 28 mean sleep scores for 21 patients were 3.3 (SD=3.0) as compared to 5.2 (SD = 2.5) at baseline, p = 0.005.

In researching the effectiveness of methylphenidate on reducing opioid-induced sedation, we discovered that methylphenidate also improves neurocognitive motor function [23]. In a double-blind crossover trial of twenty patients, we found that patients receiving methylphenidate were able to perform significantly better in neurocognitive motor functions such as finger taping and arithmetic [23]. These data are shown in the table 4 below.

Table 4: Effects of Methylphenidate on Neurocognitive Motor Tasks

Neurocognitive Task	Placebo Group	Methylphenidate	*P*
Finger Tapping (speed = 10 sec)	89 ±12	119 ±16	<0.001
Finger Tapping (speed = 30 sec)	98 ±15	130 ±19	<0.001
Arithmetic	108 ±17	78 ±21	<0.01
Reverse Digits	101 ±17	125 ±28	<0.001

Breitbart also found that methylphenidate improves neurocognitive motor function as measured by the trail making test A & B in patients with AIDS [28]. Also, methylphenidate might reduce subjective fatigue and improve physical activity by its effects on psychomotor activation.

RESEARCH DESIGN

This is a 2x2 factorial design randomized controlled, double blind, parallel study investigating the interaction between methylphenidate and nurse phone calls in reducing fatigue and associated symptoms in 212 patients diagnosed with metastatic, incurable cancer. Half of the patients will receive nursing telephone interventions (NTI) from 4 – 6 times in the first two weeks of study. Half will not. Half of the patients will receive methylphenidate and half will receive placebo. Patients will be assessed for fatigue, depression, anxiety, sleep disturbance, activity level, and neurocognitive motor function.

Patient Recruitment. Patients with advanced cancer will be recruited from The University of Texas M.D. Anderson Cancer Center (MDACC; a comprehensive cancer center) and Lyndon B. Johnson General Hospital (LBJ: a public hospital). Both hospitals are located in Houston, Texas, and Drs. Vicente Valero and Marlene Cohen, co-investigators, have joint appointments at both facilities. We currently conduct research protocols at both institutions. We estimate that 2/3 of patients will be recruited from MDACC, and 1/3 from LBJ. At MDACC, patients will be recruited from medical oncologists working in the genito-urinary, thoracic and head and neck, breast, gynecological centers, and the clinics based in our own outpatient center (pain, rehabilitation, and symptom control and palliative care clinics). We have fully established ongoing relationships with the physicians operating these clinics and they regularly refer patients to our clinical studies.

At LBJ hospital, patients will be recruited from M.D. Anderson Outreach Clinics. We have fully established research links with this clinic and we have admitted patients, especially persons from ethnically diverse groups, to our pilot study, a randomized controlled trial of methylphenidate and the nursing telephone intervention with excellent recruitment and retention rates.

MDACC's patient population is comprised of 71%, Anglos, 11% African-Americans, 10% Hispanics, and 7% other. The majority of patients have private insurance. LBJ is part of the Harris County Hospital District (HCHD), and its patient population reflects that of the 2003 data from the HCHD community. Active patients totaled 276,654, which was 11.89 % Anglo, 53.68% Hispanic, 30.39% Black, and 4.04% Asian/Other. This population is primarily indigent and uninsured with a large number of immigrants. More than half were under 200% of Federal Poverty Level in FY 2001. Recruiting from two local, yet demographically-diverse hospitals will help produce a sample that is ethnically and socio-economically representative of advanced cancer patients. Patients will be screened for eligibility criteria. Patients who are eligible and who give written informed consent to participate in this research study will be admitted to the double blind phase of the study described below. Consents forms and assessments will be available and administered in either English or Spanish (by Spanish speaking research nurse, and investigator).

Patient Compensation

Each patient that is willing to participate on this study and has signed the informed consent will receive a $10 gift card for their time and participation.

4.0 Patient Eligibility

Inclusion criteria:

1. Patients will be eligible to participate in this study if they have advanced cancer.
2. Patients will be eligible to participate in this study if they rate fatigue on the ESAS during the last 24 hours as ≥ to 4 on a 0 to 10 scale, in which 0= no fatigue and 10= worst possible fatigue.
3. Describe fatigue as being present every day for most of the day for a minimum of 2 weeks.
4. Lack clinical evidence of cognitive failure, with normal Mini Mental State Examination (MMSE). A score of 24 is considered normal.
5. Are 18 years or older.
6. Are willing to keep a daily diary, engage in telephone follow up with a nurse every other day, and return for a follow-up visit after 14 days of treatment.
7. Have telephone access to be contacted by the research nurse. If patient is relocating within 5 weeks, patient will be asked to provide a new telephone number.
8. Hemoglobin of ≥8 g/dL within 2 weeks of enrollment. If the patient has not had blood drawn for a hemoglobin level in the past two weeks, one will be done to determine the eligibility. Patients with a hemoglobin <8 will be referred for treatment of their anemia.
9. Able to understand the description of the study and give written informed consent.
10. Able to understand the description of assessments, and able to complete baseline assessment
11. Patients on no erythropoietin or on a stable dose.

Exclusion criteria:

1. Major contraindication to methylphenidate i.e. hypersensitivity, anxiety, tension, agitation, or motor tics**,** glaucoma, severe angina pectoris, or hypertension, etc.
2. Currently on methylphenidate or has been on methylphenidate within the last 10 days.
3. Inability to complete the baseline assessment forms or to understand the recommendations for participation in the study.
4. Major depression according to the S/CID DSM IV diagnostic criteria. These patients will be referred immediately to psychiatry for assessment and management.
5. Pregnant or lactating women.
6. Requirement for MAO inhibitors, tricyclic antidepressants or clonidine.
7. Glaucoma, history of marked anxiety disorders.
8. History of alcohol (CAGE questionnaire score for the last 2 years is 2 or above on a 0 to 4 scale) or substance abuse including illegal drugs and/or medications.
9. Tourette's syndrome
10. Symptomatic tachycardia and uncontrolled hypertension
11. Currently receiving oral anticoagulants (Coumadin/warfarin), anticonvulsants (Phenobarbital, diphenylhydantione, primidone), phenylbutazone, MAOIs and tricyclic drugs (imipramine, clomipramine, desipramine).
12. Patients with pacemakers
13. Patients with symptomatic cardiac arrhythmias

Randomization. Patients will be randomized at the time of randomization by accrual site to ensure an approximately equal representation of patients in each arm, by site. Separately for each site, patients will be randomized to one of the four treatment arms. The randomization schema will be based on parameters input into RANLST, a randomization program developed at MDACC and supported by an NCI grant. Initially a randomization list containing order information for all four arms will be made. Information about drug assignment will then be deleted from the list given to research nurses and information about nurse phone calls will be deleted from the file given the pharmacists.

Patient names in sequence will be recorded on each list as the patients are entered and both lists will match patient name and identification number. Only the primary statistician will know the complete list of the order of randomization into the four arms until the end of the study. In addition, the dispensing pharmacist at each site will know the randomization of drug treatment at their site and the research nurse(s) who call patients will know which patients to call. However, the code for an individual patient as to drug

treatment group may be disclosed early and the patient removed from the study in the case of a request by the primary treating physician due to adverse events. Otherwise, no other persons will know about the assignment of patients to treatment arms until the end of the study.

5.0 Study Plan and Assessment Measures

5.1 Study Plan

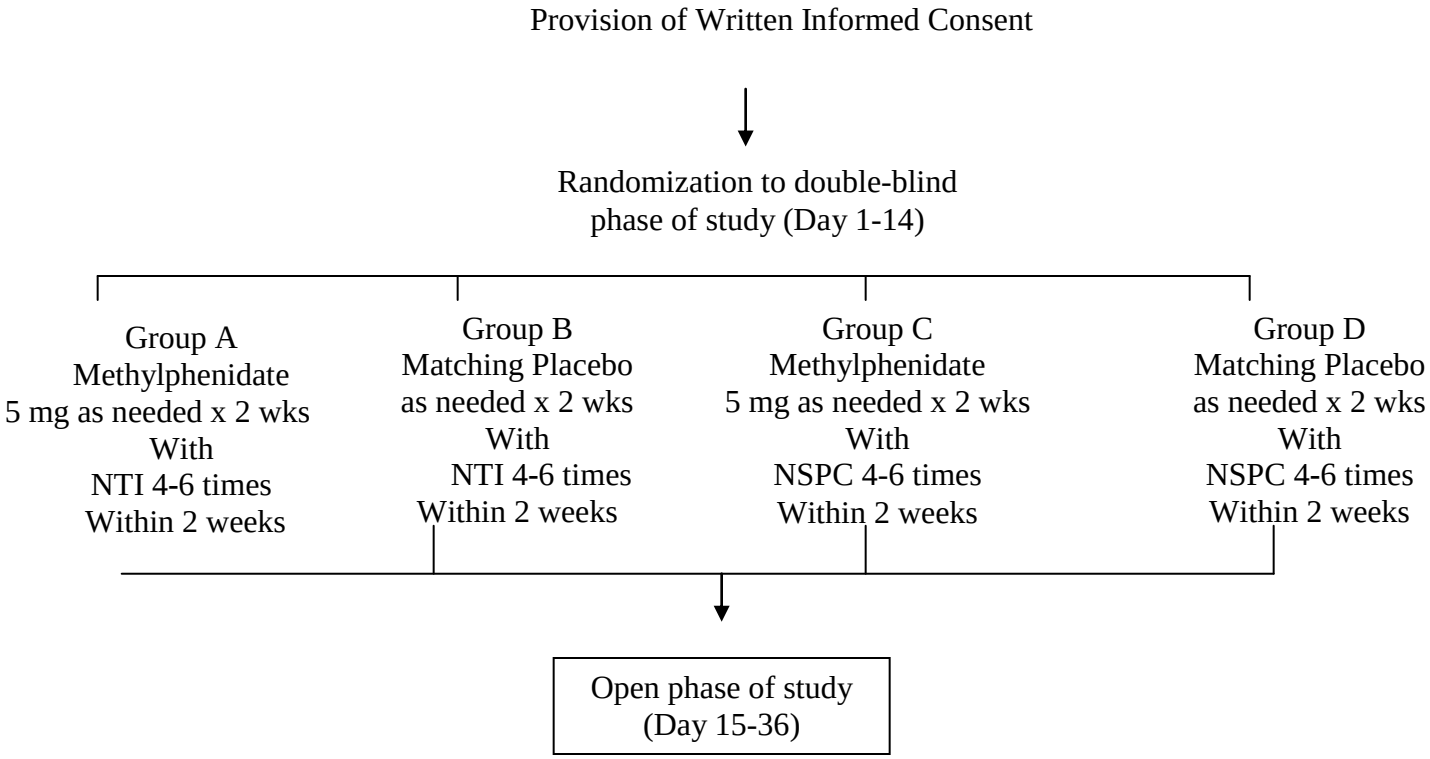
Clinical Trial Design. This will be a randomized controlled, double blind, parallel study investigating the interaction between methylphenidate and nursing telephone intervention in reducing fatigue and associated symptoms in advanced cancer patients. An overview of the study design is illustrated in Figure 3.
Double Blind Phase (Day 1-14): Patients will be randomized to one of four experimental groups receiving the treatments detailed below.

Group 1: Methylphenidate 5 mg (one capsule) orally every two hours as needed up to a maximum of 20 mg per day for a period of 14 days with nursing follow up phone call (NTI) 4-6 times during the first 2 weeks.
Group 2: Placebo, one capsule, orally every two hours as needed up to a maximum of 4 capsules per day for a period of 14 days with nursing follow up phone call (NTI) 4-6 times during the first 2 weeks.
Group 3: Methylphenidate 5 mg (one capsule) orally every two hours as needed up to a total of 20mg per day for 14 days with no specific phone calls (NSPC)4-6 times during the first 2 weeks.
Group 4: Placebo, one capsule, orally every two hours as needed up to a total of 20mg per day for 14 days with no specific phone calls (NSPC) 4-6 times during the first 2 weeks.

Open Phase (Day 15-36): The intervention phase will be followed by an open phase that will begin after the assessment at time point 2. On Day 15, all patients will be provided the opportunity to receive methylphenidate 5 mg orally as needed up to a total of 20 mg per day until Day 36. Patients will not be told whether they previously received placebo or methylphenidate. Assessments of fatigue, physical activity, and psychosocial functioning will be conducted at day baseline, day 15 (±3 days), and day 36 (±3 days). On Day 36 (±3 days) the study will be completed and patients will be referred back to their primary care physician who will discuss with the patient the appropriateness of continuing on methylphenidate.

The open phase of the study will allow all participants to receive the potential benefits from methylphenidate, and will provide important preliminary information on longer term beneficial effects and side effects from methylphenidate. Our preliminary randomized controlled trial [132] found that the improvement in 3 out of 4 items in the Functional Assessment for Chronic Therapy-General (FACT- G), and 7 out of 10 symptoms of the Edmonton Symptom Assessment System (ESAS) was maintained during the open phase at day 36. In this study, if methylphenidate is found to be useful in the population under study, this drug will be used for weeks or months. We would like to gain preliminary data about the effectiveness and tolerability over time. Some specific questions regarding the longer term use of methylphenidate include: 1) Will dose escalation be needed for patients over time? 2) Will patients find the drug less useful and therefore decrease utilization over time? 3) Will the global assessment of treatment effectiveness decrease over time? 4) Will there be new or more severe side effects in this patient group over time? The preliminary information gained during the open phase will help us better delineate the overall role of methylphenidate in the long term management of fatigue in advanced cancer.

Figure 3. Study Design



Methylphenidate Treatment. Methylphenidate is a central nervous system (CNS) stimulant. This drug is usually very well tolerated when used in advanced cancer patients (38, 53-54), when used long term in attention deficit disorder (74-75) and when used in the management of depression in the elderly (25, 76). The dose of 5 mg orally and the modality of administration on an "as needed" basis has been chosen because it was found to be effective and well tolerated in our pilot study [38]. We also extended the double-blind treatment phase to 14 days to more effectively rule out placebo effects. Breitbart's findings [28] indicated differences between placebo and treatment groups after 14 days on a standardized comprehensive fatigue assessment scale (Piper Fatigue Rating Scale), similar in design to the fatigue measure (FACIT-F fatigue subscale) to be used in the proposed study. However, considering the attrition rate in our pilot and Breitbart's, we chose a study length that we believed would not be impacted by the attrition factors observed in previous studies with advanced cancer patients. Placebos matching methylphenidate will be made in the pharmacy of MD Anderson Cancer Center. In the double blind phase, capsules and lactose will be used for the placebos, and capsules and methylphenidate will be used for the study drug. Both groups will receive a 14-day supply of medication. Patients will be instructed on how to take the medication. They will also be provided dosage recommendations and potential side effects. Patients will be given a diary to record daily dosage. The research nurse will monitor the medication usage via diary records.

During the double blind phase, all patients will be provided with a 14-day supply of methylphenidate or placebo by the pharmacy at MDACC. The randomization code will be kept in the pharmacy and will only be broken for the final analysis upon completion of patient accrual. In cases of serious toxicity the principal investigator will be able to request that the code be broken for a specific patient. On Day 15, patients who choose to continue methylphenidate will be given a three-week supply. The medication will be provided free of charge.

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.

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

chest pain (possibly due to heart trouble)
high blood pressure
low blood pressure
irregular heartbeat
fast heartbeat
slow heartbeat
extra heartbeats
inflammation of arteries in the brain
blocked blood vessels in the brain
heart attack
abnormal heart sound due to turbulent blood flow
blood vessel disorder causing cold, numb, and discolored fingers and/or toes
aggression, irritability, and/or anger
agitation and/or anxiety
confusion
depression
dizziness
fatigue, drowsiness, and/or tiredness
fever
headache
difficulty sleeping
mood alterations
nervousness, tension, and/or restlessness
condition that results in muscle stiffness, high fever, and/or drowsiness
stroke
Tourette's syndrome (uncontrolled speech and/or muscle movements)
psychosis (loss of contact with reality)
hallucinations
mood disorder with extremes of happiness and sadness
seizures
hair loss
shedding and scaling of the skin
increased sweating
skin rash
hives
skin redness
painful menstruation
stunted growth
abdominal pain
decreased appetite
grinding or clenching of teeth
constipation
diarrhea
upset stomach
nausea
vomiting
weight loss
dry mouth
spots under the skin caused by bleeding
inability to have an erection
decreased sex drive
blood vessel inflammation (possible fever and/or fatigue)
jaundice (yellowing and/or darkening of the skin)
abnormal liver tests (possible liver damage)
joint pain
uncontrolled movements
muscle tightness
tickling/tingling sensation
muscle twitching
blurred vision
dry eyes
pupil dilation
vision problems
double vision
cough
difficulty breathing
sore and/or painful throat
inflammation in the nose
inflammation of the sinuses
head cold
allergic reaction

Methylphenidate may cause low blood cell counts (white blood cells, red blood cells, and platelets). This means that while you take the drug, there is more of a chance of getting an infection, including pneumonia. You may become anemic and/or have problems with bleeding, bruising, fatigue, and/or shortness of breath. You may need a blood transfusion. All patients will be provided with a toxicity-recording sheet. Patients will be instructed to record side effects daily.

For those who receive NTI, the research nurse will assess toxicity during NTI. For those who receive NSPC, toxicity will be assessed by the research nurse once a week for 5 weeks. All patients will be provided with the research nurse contact phone number, MD Anderson Cancer Center emergency center telephone number, LBJ hospital emergency room telephone number, and will be asked to immediately call staff members if they perceive any serious or unusual side effect.

Drug Dependence. Methylphenidate has been abused and it has addictive potential [32]. Our group has conducted five trials of methylphenidate [22, 23, 38, and 54] and preliminary data reported above], 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.

Patients will be instructed that capsules should not be opened or crushed. Methylphenidate should be taken only as prescribed and should be given cautiously to emotionally unstable patients, such as those with a history of drug dependence or alcoholism, because such patients may increase dosage on their own initiative. Chronically abusive use can lead to marked tolerance and psychic dependence with varying degree of abnormal behavior. Careful supervision is required during drug withdrawal, since severe depression as well as the effects of chronic over activity can be unmasked. All patients on this study will be educated about the abuse potential of methylphenidate. The research nurse as routine M.D. Anderson Cancer Center protocol procedure will conduct weekly pill count. During the double blind phase, only 2-week drug supply will be provided, and during the open phase, a 3-week drug supply will be provided.

Potential withdrawal symptoms and intervention The most frequent problems associated with the withdrawal of methylphenidate are the return of the symptoms for which patients were originally treated. For example, there may be aggravation of symptoms of attention deficit hyperactivity disorder or depression. Other possible symptoms would include an aggravation of somnolence and/or fatigue [131]. However, our group has conducted five trials of methylphenidate (daily dose ranges from 10 mg to 20 mg) in cancer patients followed by discontinuation [22-23, 38, 53,132], we did not observe any cases of withdrawal symptoms. Other investigators also observed similar findings. Arnold et al. conducted a 2-week double-blind, placebo-controlled withdrawal trial of methylphenidate in 76 evaluable children with attention deficit hyperactivity disorder (ADHD). They noticed no withdrawal signs and symptoms [128]. Nalon et al. switched from methylphenidate to placebo under double-blind conditions in 17 children with ADHD and chronic tic disorders [129], and found no signs of withdrawal. In a double-blind randomized placebo-controlled crossover study of 60 patients with chronic fatigue syndrome, Blockmans et al. did not observe withdrawal symptoms after patients received 4-week methylphenidate and crossed over to 4-week placebo [130]. Breitbart and colleagues in their study of 109 HIV patients receiving methylphenidate versus pemoline for the treatment of fatigue found no withdrawal symptoms after 6-week trial [28].

Regardless, all patients are instructed to report to the research nurse if any of withdrawal symptoms develop, and appropriate interventions will be initiated by the research nurse. All patients who drop out of the study and all patients who discontinue methylphenidate after the completion of the open label phase will receive a weekly phone call from the research nurse regarding the presence of aggravation of depression, somnolence, fatigue, or other symptoms of withdrawal. These telephone calls will continue for a period of four weeks. If patients are found to develop any of these acute withdrawal symptoms, the patients will be immediately referred to their primary care physician and/or the emergency room at M. D. Anderson or Lyndon B. Johnson Hospital will be made, respectively, and the primary care physician and the emergency room physician will be notified of these findings for appropriate clinical management.

Nursing telephone intervention (NTI). All patients randomized to receive NTI will be contacted by a research nurse with training in palliative care 4-6 times during the first 2 weeks of the treatment. Those who are randomized to receive NSPC will be contacted by a non-nursing person 4-6 times during the first 2 weeks. The nurse will contact the patients at a time agreed upon during the initial meeting. Conversations with nurses will be standardized in terms of questions that the nurses ask of patients, and attempts will be made to ensure consistency of time spent talking with patients. The phone calls will begin with a brief 1-minute introduction and statement of the purpose of the phone call. NTI will include:

1. Assessment of symptoms using M.D. Anderson Symptom Inventory (MDASI);
2. Assessment of toxicity using a toxicity record sheet;
3. Review of medication including regular and as needed medication;
4. Provision of psychosocial support and patient education.

MDASI is a brief, easily understood instrument, which provides a measure of the intensities of 13 cancer-related symptoms. Patients rate the intensity on 0 to 10 numerical scales from "not present" to "as bad as you can imagine." A Spanish version of the MDASI has been developed, by translating and back translating the instrument to check the translation. Validation of the instrument has been completed (77). The research nurse will address main symptoms in the order of severity as recorded on the MDASI. Research nurse counseling will proceed according to the Methylphenidate and Nursing Intervention for Cancer Related Fatigue Study Manual (Appendix U). Research nurses will ask what additional symptoms patients may have experienced during the last few days. Patients will also be asked about any side effects they may have experienced and the severity of those side effects, based on NCI Common Toxicity Criteria, while taking methylphenidate. The research nurse will review medications, including type and dose of all regular and "as needed drugs", and provide educational advice as needed. The research nurse will also ask open-ended questions regarding general well being of the patient and family. The research nurse will provide empathetic listening, answer all the questions, and provide supportive statements and end the telephone call.

If necessary or appropriate (i.e., in the case of severe symptoms), the nurse will contact a physician and phone the patient with recommendations or will recommend that the patient come to the hospital. The total duration of the phone call is expected to be less than 30 minutes according to our experience in previous studies [38].

In this study, 106 patients will be involved in the NTI, each called longitudinally at 4 to 6 times or 424 to 636 calls. The telephone conversation between the nurse and the patient will be recorded using a recording devise M. Cohen has used in prior research. These calls will produce qualitative data that are useful to understand and identify interventions that are appropriate for phenomena that change over time, as do symptoms for persons with advanced cancer. Content analysis will be conducted on transcripts of the telephone interviews with the nurses, and with the open-ended questions in the outcome assessment. Content analysis is one aspect of phenomenological work, with which Cohen has extensive experience. While the data obtained is not precisely the same as phenomenological data, there are many similarities, and we anticipate that data will elucidate the meaning of the experiences of both the symptoms and the intervention.

As is done in phenomenological research, data analysis will occur simultaneously with data collection. The goal of analysis will be a thick description. A thick description is one that captures the experience from the perspective of the informant in its fullest and richest complexity (78). This analysis will provide a detailed description of the meaning of both intervention and patients' symptoms.

Data management: Cohen, with the help of the research nurses, will supervise and verify verbatim transcription of the audiotapes of each telephone intervention. The transcriptionist will use a common editorial software program such as Microsoft Word for transcription.

Data collected in the course of the nursing telephone interventions will be used for the purposes of ensuring the quality and consistency of the nursing intervention, such as determining if education and psychosocial support are appropriate and consistent, and for qualitative analysis.

Training of Nurses. The research nurses conducting telephone interventions will undergo a training program conducted by the principal investigator [EB], the research manager [JW], and the nurse specialist [MC]. The training program will include 40 hours of structured training and consist of lectures, role play, and discussion in all aspects of the appropriate assessment of the different symptoms, how to follow the different guidelines for the management of the most common symptoms according to the Methylphenidate and

Nursing Telephone Intervention for Cancer Fatigue Study Manual [Appendix U]. The manual includes Research Nurse Training Curriculum, Weekly Research Nurse Refresher Curriculum, and information on Methylphenidate, the Nursing Telephone Intervention information and Symptom Assessment and Management. The training also includes elements for expressive supportive counseling as regularly conducted by our palliative care program. Mock telephone interviews will be included in the training, and will be recorded, reviewed, critiqued, and discussed. Training on the other study instruments will consist of several mock interviews that will be observed and critiqued. The research nurses will evaluate study patients only after they have successfully completed training.

Areas of interviewing that will be addressed in the training will include reducing interviewer bias, preventing the introduction of assumptions and leading statements, reflecting informants' views rather than suggesting views, and helping informants elaborate on and clarify their perceptions. M. Cohen will continue to review the audiotapes and discuss them with the interviewers throughout the project. This procedure discussed by Tripp-Reimer (79) and used by Cohen in prior research, has been successful in obtaining rich phenomenological data. The techniques in phenomenological interviewing are exactly what are required in the NTI.

Weekly Research Nurse Refresher Curriculum. Every week there will be a session of not less than two hours and 15 minutes with the project manager and the PI to discuss methylphenidate and pharmacy procedures, review the NTI, including quality assurance of tape recorded nursing interventions, discuss problems and solution related to symptom assessment and management, methylphenidate and the nursing intervention, patient drop outs and missing data. The research nurses will also discuss the progress of the different telephone calls and during these weekly meetings there will be booster sessions on different specific aspects of how to conduct symptom assessment, algorithms for symptom management, and expressive supportive therapy. Nurses will be encouraged to ask questions and when appropriate other investigators will be invited to the weekly sessions for further clarifications.

Quality Assurance. All interviews will be tape-recorded. The research manager will conduct weekly quality improvement with all the research nurses by discussing the content of the NTI. Focus will be made on appropriate techniques for symptom assessment, appropriate advice based on the use of the algorithms, and the quantity and quality of expressive supportive counseling. M. Cohen, who will be analyzing these transcribed interventions, will also alert the research manager and staff should problems be noted in the techniques the nurses are using. She will meet with the research nurses to discuss any changes in the quality or consistency of these calls.

5.2 The following assessment measures will take place at baseline and during the study (see table 5):

Pre-Treatment Assessments. The assessment of demographic variables will include patient self-reported birth date, gender, marital status, ethnicity, education, and job status, primary cancer, cancer treatment within the last year, surgery, chemotherapy, immunotherapy or radiotherapy, and medications including opioid dosage.

Baseline assessments of symptoms include FACIT-F (including FACT-G and Fatigue subscale), Hospital Anxiety & Depression Inventory (HADS), Edmonton Symptom Assessment System (ESAS), and Six-Minute Walk test, Symbol Digit Modalities Test (SDMT), Pittsburgh Sleep Quality Index (PSQI).

Outcomes Assessments:

5.3 Fatigue. The Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) is a subscale of the Functional Assessment of Chronic Illness-General scale and has been used primarily in cancer patients to measure fatigue during the past 7 days. The subscale consists of 13 items. Test-retest reliability coefficients for the fatigue subscale have ranged from 0.84 – 0.90. This scale has also demonstrated strong internal consistency (alpha = 0.93-0.95) [80]. This measure is available and validated in Spanish.

5.4 Number of Pills Taken. The number of methylphenidate and placebo pills taken over the course of the study will be recorded. As we expect the methylphenidate pills to have greater efficacy in the treatment of fatigue, we hypothesize that patients will take more methylphenidate pills than placebo pills.

5.5 Depression and Anxiety. Depressive and anxious symptoms will be assessed using the 14-item Hospital Anxiety and Depression (HADS) questionnaire [81]. This questionnaire has been found to be valid

and reliable in a number of clinical situations and has been widely used in medically ill patients. Although its use in cancer patients has been somewhat limited, we believe its proven validity in the clinical setting makes it well suited for our study. This questionnaire asks patients to underline the statement that is closest to how patients have been feeling in the past week. This measure is available and validated in Spanish.

5.6 Other Common Symptoms. The Edmonton Symptom Assessment (ESAS) measures the patient's response to ten common symptoms in the past 24 hours (pain, fatigue, nausea, depression, anxiety, drowsiness, and shortness of breath, appetite, sleep, and feeling of well being) in patients with cancer or other chronic illnesses. This questionnaire has been found to valid and reliable in cancer populations [82] and it is available in Spanish.

5.7 Sleep Disturbance. Sleep disturbances will be assessed using the Pittsburgh Sleep Quality Index (PSQI) [83] and the Pittsburgh Sleep Diary (PghSD) [83]. The Pittsburgh Sleep Quality Index is an 18-item self-report measure. Patients will be asked to report their usual sleep habit during the past 2 weeks. This instrument provides a brief, clinically useful assessment of a variety of sleep disturbances that might affect sleep quality over a one-month period. We will modify the time period to two weeks. A total score is derived, as well as seven subscales consisting of subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medications, and daytime dysfunction. The PSQI has good internal (0.83) and test-retest reliability (0.65-0.85). The PSQI was found to have good validity, and for distinguishing between patients with depression, disorder of initiating and maintaining sleep, disorder of somnolence, and healthy controls. Validity of the PSQI is supported by significant differences between "good" and "poor" sleepers' PSQI global and component scores; a sensitivity of 89.6% and specificity of 86.5% using a cut-off score of 5 to identify a sleep disorder; and by similar group differences in terms of PSQI scores and polysomnographic sleep measures. This assessment tool is available in Spanish.

The PghSD was developed as a diary of sleep-wake behavior that could be used easily by research subjects and patients [79]. It comprises a bedtime and wake-time assessment. We will collect sleep diary data for 7 consecutive days during the time the actigraphy data are being collected. The bedtime portion of the diary asks questions about the times of meals, naps, exercise, and medications, and about the consumption of caffeine and alcohol and tobacco use. We have modified the diary to also include six common cancer-related symptoms: fatigue, nausea, pain, anxiety/tension, blue/down, and difficulty thinking. The wake-time portion of the diary asks the patient to record aspects of the previous nights sleep; symptoms they may have had during the night (nausea, pain, anxiety, and worry); and upon awakening a rating of whether they feel rested, blue/down, and anxious. The PghSD has been used by the sleep laboratory in Pittsburgh for over a decade and has been adopted by several other researchers. The PghSD is sensitive to differences between young and old individuals, and between patients with sleep disorders and healthy controls [84]. Sleep diary data will be used to quantify (1) subjective sleep quality; (2) self-reported sleep duration, latency, and fragmentation; and (3) sleep-related behaviors. Data will also be used to help verify actigraphy-derived data regarding of sleep duration and fragmentation. Summary scores will be calculated for diary data, although repeated measures analyses of daily data will also be done. The PghSD takes less than 2 minutes to complete upon awakening and each evening at bedtime.

5.8 Physical Activity. The six-minute walk test will be used to assess physical function and has been recommended by the American Thoracic Society (ATS) as an objective measure of functional capacity [85]. This test has been found to be an objective measure of functional capacity in patients with chronic respiratory conditions, fibromyalgia, stroke, and cancer [85]. Our group has used this methodology in the assessment of fatigue and dyspnea [86]. Assessment will occur at baseline, day 15 and day 36. The standardized protocol for administering this test will be followed. The Borg scale will be used to assess fatigue and shortness of breath prior to the six-minute walk and at the end of the walk [85]. Our previous study demonstrated that 6-minute walk in patients with fatigue and dyspnea related to lung cancer was well tolerated. 33/33 (100%) patients were able to tolerate two episodes of 6-minute walks within half hour [86].

In the proposed study establishing a baseline pattern of activity and sleep before the activation of the clinical trial would be optimal in order to compare changes in activity levels after the intervention, however, logistically this is not possible. To establish baseline patterns would necessitate a delay in administering the intervention to eligible patients recruited during 2 clinic visits and would require an additional clinic visit to begin the intervention. This would be an additional burden to the patient and might deter recruitment efforts.

Another way to address this problem might be to visit the patient in the home. However, visiting the patient in the home would confound the testing of our hypothesis about the therapeutic value of nursing telephone interventions. Thus, we will record activity over the fourteen-day intervention period. Our group has conducted a pilot study with Actigraph and has extensively consulted with colleagues who have conducted this research. We believe that Actigraph has shown the ability to receive reliable 24-hour and awake/asleep data as well as overall activity. We hypothesize that patients receiving methylphenidate will significantly and progressively increase their mean activity and decrease their percent sleep during the "out of bed" portion of the day as compared to the placebo group.

All patients will carry a wrist actigraph monitor for the 14-day period of the double-blind phase. Motion will be recorded 6 times per minute and the following measurements will be conducted:

a. Mean activity during the "out of bed" portion of the day;
b. Percent sleep during the "out of bed" portion of the day;
c. Number of hours of "in bed" portion of the day.

Actigraph record will be downloaded in the department specific database.

In cases that patients are unable to walk, or unable to return to clinic on the scheduled days (15+/-, or 36 +/-), 6-minute walk will not be performed.

5.9 Neurocognitive Motor Function. The Symbol Digit Modalities Test (SDMT) will be used to assess neurocognitive motor function. Our group has considerably experience with this tool. SDMT requires examinees to match numbers to a series of different symbols presented randomly on a single test page, using a key found at the top. There are 120 matches to be made in total, and each subject has to make as many as possible, working in a consistent order, within a 90 second period. The score is the number of correct matches in the 90-second period, excluding the 10 practice items. It is recorded as a proportion of the total number of responses, for example 36/39 indicates that the examinee made a total number of 39 responses, 36 correct and 3 incorrect. This gives a measure of both speed and accuracy. It is possible to convert the raw score into a standard score, with a mean of 100 and a standard deviation of 15. It is a useful diagnostic tool, measuring clerical speed, visual search and memory, fine motor control and concentration (87). In our donepezil pilot study for opioids induced sedation [13] and a current randomized, double blind controlled trial for cancer fatigue, adherence to SDMT has excellent. SDMT will be performed at baseline, and on days 15 and 36 (+/-3 days). In cases that patient is not able to complete the assessment as scheduled (i.e. Unable to reach patient, SDMT form is not available, severity of symptoms or refusal), SDMT will not be performed.

5.10 Quality of Life. The Functional Assessment of Cancer Therapy-General (FACT-G) is a self-report measure of quality of life in people with cancer. Nearly all patients with a sixth-grade reading level can easily complete the measure without assistance. The system contains a 27-item compilation of general questions divided into four primary QOL domains: Physical Well-Being, Social/Family Well-Being, Emotional Well-Being, and Functional Well-Being. It is considered appropriate for use with patients with any form of cancer. Validation of a core measure allowed for the evolution of multiple disease, treatment, condition, and non-cancer-specific subscales [88]. FACIT-F fatigue subscale has 13 items regarding patient's fatigue during the last 7 days. Patients rate the intensity of fatigue and its related symptoms on 0 to 4 numerical scales from 0 "not at all" to 4 "very much," This tool is available and validated in Spanish.

5.11 Assessment of Blinding for Patient and Research Nurse. At the end of week 1 and week 2, both patients and the research nurse will be asked about their belief of the treatment received by the patient: 1) I believe that I (my patient) received study drug (methylphenidate); 2) I believe that I (my patient) received placebo; and 3) I don't know.

5.12 Global Assessment of Effectiveness of the Treatment. This instrument will estimate the minimal important difference in patient's overall symptom perception before treatment and after treatment. Patients will be asked about their symptom perception after starting the new medication. 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 tool has been widely used in symptom research [89-90]. We will

also use the "was it worthwhile?" assessment of participation in the clinical trial, developed by Sloan et al (91).

5.13 Medication Review. Patients receiving opioid analgesics (approximately 80% of patients with advanced cancer) will be eligible for this study. The type, route, and daily dose of opioid analgesics will be recorded from information given by the patient on a weekly basis. This will include regular opioid dose and extra rescue dose. Patients will be allowed to receive laxatives, antiemetics, and other symptom related medications. They will be encouraged to carefully register in the diary the medications they have taken and to contact the research nurse before making major drug modifications.

5.14 Assessment During Treatment. During treatment, patients will maintain a daily diary of their fatigue and other symptoms, the number and times pills are taken, and the fatigue rating before and 2 hours after taking methylphenidate. A research nurse will contact patients randomized to receive nursing telephone intervention 4-6 times for the first 14 days of the study. Table 5 [next page] illustrates assessments performed during study. Our preliminary data from our pilot study [38] as well as our pilot randomized controlled trial of methylphenidate plus nursing telephone interventions strongly support that patients comply with these assessments very well. (See table 5 below).

Table 5. Assessment Schedule

Time Point	Baseline	Day* 8 (±3days)	Day* 15 (±3days)	Day** 22 (±3days)	Day** 29 (±3days)	Day** 36 (±3days)
Instruments						
FACIT-F (including FACT-G)***	■		■			■
FACIT-F (subscale only)***	■	■	■	■	■	■
Hospital Anxiety & Depression Inventory (HADS)***	■		■			■
Edmonton Symptom Assessment Scale (ESAS)***	■	■	■	■	■	■
Six-Minute Walk Test	■		■			■
Symbol Digit Modality Test	■		■			■
Pittsburgh Sleep Quality Index***	■		■			■
Fatigue Diaries***		■	■			
Toxicity Assessment***		■	■	■	■	■
Global Assessment			■			■
Assessment of blinding (patient & nurse)		■	■			
Actigraph record			■			
Study drug count		■	■	■	■	■

KEY: SHADED AREAS DENOTE ASSESSMENT GIVEN AT PARTICULAR TIMEPOINT.

*Patient Diary is only provided to the patient for the first 2-week double blind phase of the study.

** During open label phase, weekly assessment of FACIT-F, ESAS, Toxicity, drug count, and current opioid will be reviewed with the patient over the phone or in the clinic.

*** These assessments are available in English and Spanish to allow recruitment and enrollment of Spanish-speaking patients.

If the research nurse is unable to reach patient after 4 attempts, or patient is unable to answer questions due to severity of symptoms or refusal on the scheduled day (+/- 3 days), the research nurse will dictate in the progress notes detailing this effort, but assessments will not be performed.

6.0 Statistical Considerations

Prior to inferential procedures, extensive descriptive statistical analyses of the outcome and predictor variables will be conducted. Standard descriptive statistics including means, standard deviations, ranges, and frequencies, together with 95% confidence intervals, will be computed where appropriate. Distributional characteristics of relevant variables will also be more closely examined using box plots and histograms. If the data do not appear to be approximately normally distributed, transformations will be made to the data. Bivariate associations will be explored using Pearson's Product Moment correlation coefficients, scatter plots, and contingency tables.

The primary endpoint of the study is the difference between the FACIT-F Fatigue Sub Score at baseline and 15 days later. The goal of this study is to detect average difference scores of approximately 33% from baseline for methylphenidate versus placebo or between every other day NTI versus no NTI or 50% or more between any arms of the study. The total sample size will be 212 patients.

We base this estimate in part on our previous study [38] that found close to 100% reduction in fatigue (baseline 17.5 to 34.7) by seven days in a group of 30 patients receiving methylphenidate and research nurse phone calls. We expect little reduction in fatigue for patients receiving placebo and no research nurse phone calls at 15 days, although there could be some placebo effect. We expect that the other two arms will fall somewhere in between.

As previously described, the four arms of the study are A) methylphenidate plus RN phone call, 4 – 6 times in the first 2 weeks of study, B) placebo plus RN phone call 4 – 6 times in the first 2 weeks of study, C) methylphenidate plus no phone call, and D) placebo plus no phone call. An advantage of the structure of our arms, which is a factorial treatment structure, is that it provides the opportunity for testing for significant differences between methylphenidate versus placebo and between 4 - 6 NTI versus no NTI; and also between all four arms of the study [92]. The design also allows us to test the synergistic effect of both phone calls and methylphenidate.

The effect of the interventions on fatigue, physiological symptoms, and psychological symptoms will be tested using ANCOVA in SAS (SAS Institute, Cary, NC). The fatigue outcome variable will be regressed onto the treatment group variables (two main effects of RN phone call and methylphenidate, each with two subgroups) with covariance adjustment for the baseline value of the outcome variable. Standard residuals-based diagnostic procedures will be used to test model assumptions and influential observations. Normalizing or variance stabilizing transformations will be made as necessary. Although the randomization procedure will most likely ensure that these simple treatment comparisons are valid, additional covariance adjustments will be included in the models for age, gender, socioeconomic status, and ethnicity. These variables will be forced in the model in a single step. The magnitude and significance of the treatment condition variables will thus represent the effect of the interventions after adjustment for the covariates. Separate analyses will be conducted for the outcome measures for each follow-up time point. To prevent inflated Type I error rates due to multiple comparisons, p-value adjustment will be conducted using the bootstrap resampling approach described by Westfall and Young (93). This approach is less conservative than the standard Bonferroni approaches, while at the same time preserves the overall desired Type I error rate. Algorithms for this procedure are currently available in SAS.

Additional analyses will also be conducted in which all follow-up time points will be analyzed simultaneously using mixed model ANCOVA in SAS. In mixed model ANCOVA, repeated measures data can be included by including random effect regression terms that provide adjustment for the correlation structure that exists across measures from the same individual. At a minimum, a random effect term corresponding to the individual will be included in the model. Additional covariance structure among observations from the same individual will be modeled by selecting the best fitting variance-covariance matrix using the procedure described by Wolfinger (94). A separate time variable will be included in the model to allow simple trends to be tested. An interaction term between time and treatment group will be added to test for differential patterns of change across time between the two treatment conditions. Similar covariance adjustment for age, gender, socioeconomic status, and ethnicity will be included as described above.

We will initially test for the main effects of treatment (methylphenidate versus placebo) and NTI (every other day versus none) and their interaction on fatigue. If there were a significant interaction, this would mean that the two factors were not independent. If this is found to be the case, four additional comparisons will be made: between NTI with methylphenidate, NTI with placebo, no NTI with methylphenidate, and no NTI with placebo. Although not independent, these F tests are essentially least significant difference comparisons [95]. We will also use an analysis of variance to determine if any of the four arms of the study differ. If the overall F statistic from this test shows a statistical difference less than 0.05, we will then perform a set of additional pair wise comparisons using Duncan's multiple range tests [96]. If the data appear to be non-normally distributed, we will use equivalent nonparametric tests; in this case the Kruskal-Wallis test with associated multiple comparison tests [97].

In addition to fatigue, we will also test for differences between arms of the study for other continuous variables such as depression, pain, nausea, anxiety, insomnia, physical activity and neurocognitive motor function, using the same statistical methods as used for fatigue. Given the available sample size, changes between baseline and day 15 that are at least as large as 60% of the associated standard deviation will be declared statistically significant at a two-sided significance level with 80% power. When the arms for treatment/no treatment are combined or phone call/no phone call, the differences that can be detected between groups will be 42% or greater of the standard deviation.

We will also have weekly information available for ESAS scores of fatigue, pain, etc. Therefore we will also test, on an exploratory basis, for trends over time for each of these variables using repeated measures analysis of variance. We will attempt to determine if there are differences by arm for these trends. However, since fatigue scores may not linearly decrease over time, this method of analysis may not be justified. We expect that fatigue scores will rapidly be reduced in the methylphenidate arms and that this reduction will be maintained over time. We also expect that fatigue scores in the placebo/no phone call arm will include some placebo effect of reduction in fatigue initially, but do not expect that this reduction will continue throughout the study. We expect that the other two arms will fall somewhere in between these two extremes. As summary measures, we will, at minimum, calculate average fatigue scores and standard deviations by group at each time point.

We will also summarize the number of capsules taken by patients at days 8 and 15. We expect that patients randomized to placebo will be taking fewer capsules at these two times, due to realizing that the capsules are not working, than patients randomized to methylphenidate. We will compare these numbers by arm using either an analysis of variance or a Kruskal-Wallis test, depending on the distribution of the data.

Variables with percentage outcomes (such as percent sleep during the "out of bed" portion of the day) will be analyzed at specific time points (baseline and 15 days) using chi-square analyses or binomial tests to compare arms.

We will also determine if number of phone calls (NTI or NSPC) or the group assignment (phone calls versus no phone calls) interacts when predicting quality of life, fatigue-related symptoms, and fatigue. We believe that patients receiving phone calls will experience improved quality of life, reduced fatigue-related symptoms, and reduced fatigue while the patients not receiving phone calls will remain the same on these scores. In this model we will also include the treatment group assignment to determine if these interactions differ by treatment group.

Missing Data. In order to allow for up to 15% of the patients to potentially drop out before completing the

study for 15 days, we will recruit a total of 53 patients per arm, or a total of 212 patients. After 7 days of our open pilot study of methylphenidate [38] we found that 30 out of 31 eligible patients were evaluable (97%). By day 28, only 21-30 patients remained evaluable (70%). Therefore, we estimate that the drop out rate could increase from 3% by day 7 to 30% by day 28. Since the duration of this study is of 15 days, we conservatively estimate that the dropout rate will be approximately 15% upon completion of the double-blind phase.

Information from the intervention phase (days 15-36), where all willing patients will receive study drug, will be summarized and exploratory analyses conducted to determine if patients in the treatment group continue to experience reduced fatigue and if patients previously assigned placebo improve. However, the dropout rate after 15 days could be greater than 30% and sicker patients may be more likely to drop out early. Therefore the conclusions from these analyses may be preliminary only. However, this data set will also be used to determine the impact of different methods of taking into account data that may not be missing at random.

As an alternative analysis, subjects who drop out during the study will have their last available scores from the outcomes measures carried forward. This procedure will be used because subjects may in some cases drop out because of worsening disease, which may be reflected in their fatigue measures. Failure to account for this might otherwise bias the treatment effect estimate.

We will initially assume that missing data will give unbiased estimates of the intervention effects provided that the probability of having missing data depends only on the covariates in the model. We will check this assumption by looking at predictors of missing data. If the assumption is violated we will perform sensitivity analyses to determine the effect of varying the assumptions about the mechanisms for missing data. Other methods of accounting for missing variables will also be employed in sensitivity analyses (98).

Model Analyses. Structural Equation Modeling (SEM) will be used to test for mediation and or moderation of the interventions. The model presented in Figure 1 will be formally evaluated, as will more complex forms of the same model that include repeated measures of the outcome variables across time. To test mediation an approach based on the work of Kenny and colleagues (99-100) and further extended by MacKinnon (101) and Brown (102) will be used. In order for the proposed mediators to mediate the effects of the interventions, four separate criteria must be met:

1. the interventions must be significantly associated with the outcome measures of fatigue;
2. the interventions must be significantly associated with the mediators;
3. the mediators must be significantly associated with the physiological and psychological symptoms; and
4. the association between the interventions and the outcome variables must decrease in the presence of the mediators.

The mediation effect estimate will be computed according to MacKinnon (100) who describes mediation as the difference of the treatment condition with and without the presence of the mediators, or alternatively, the product of the effect of the treatment on the mediators and the mediators on the outcome controlling for the treatment. Though mediation is often assessed using a sequence of independent regression equations, this practice becomes cumbersome in tests of complex theoretical models and is now often examined using SEM (102). In accordance with the methodology detailed by MacKinnon (101) and Brown (102), the four criteria to assess mediation will be examined in simultaneous model and parameter tests using SEM software (e.g., EQS, Mplus, AMOS).

Moderation will be examined by including interaction terms between the treatment group variable and the potential moderators. SEM provides a flexible approach to modeling means, covariance, and correlation structures that yields relevant effect estimates (directional and non-directional; direct, indirect, and total) and standard errors for all of the parameters of interest in mediator analyses (101-103). SEM also allows outcome measures obtained at all of the follow-up time points to be included in the same model. In this approach, potential mediators can be evaluated at individual time points, or averaged across time, or can be grouped together with other mediators to evaluate combined effects. Furthermore, beyond providing tests of model parameters, SEM also provides global measures of model fit (104); and permits the incorporation of latent variables into mediator models when appropriate (103-105). In addition, recent versions of software

such as EQS permit robust model and parameter assessment under varied distributional conditions (102-106).

Power Considerations. The study is powered to be able to detect significant differences of change scores as large or larger than 33% or more from baseline to day 15 between methylphenidate versus placebo. For the first secondary objective, it will be able to detect significant differences of change scores as large or larger than 33% or more from baseline to day 15 between the 4-6 phone calls (NTI) with a nurse versus no phone calls with a nurse. For the second secondary objective, it will be able to detect 50% or more change from baseline to day 15 between any of the four arms of the study. Smaller differences will be able to be detected for the first comparisons since two arms will be combined for each of those comparison groups.

The actual difference score related to a 33% or more change from a baseline of 17.5 is about 5.8, and a change of 50% or more is 8.75. Previous research has shown that a difference of 5 or greater is the "minimally important difference" required to determine that the observed change in fatigue scores is significant [107]. Assuming that the standard deviations of these difference scores are approximately equal to the standard deviation of differences found in our previous study (13.96), we will require 45 evaluable patients per each of the four arms in order to detect these differences with 80% power and a two-sided significance level of 0.05.

We also estimate power in terms of Effect Size Index (ESI), which renders the detectable difference in terms of population standard deviation units (108). For example, an ESI of 0.5 represents an effect size of 0.5 standard deviation units. We anticipate that we will be able to recruit approximately 212 participants during the recruitment period. With a maximum attrition rate of 15% by the 15-day follow-up, we will have approximately 45 participants per each of the four groups available for analysis. Using a simple t-test for two main effects comparisons at the 15-day follow-up and assuming a two-tailed type I error rate of 0.05 and a sample size of 90 participants per each main effects group, we will have 80% power to detect a true effect size of 0.42 standard deviation units. By the end of the study, at 36 days, we may experience up to a 30% dropout rate, or have 74 patients per each main effects group remaining in the study. Using a simple t-test for two main effects comparisons at the 36-day follow-up and assuming a two-tailed type I error rate of 0.05 and a sample size of 74 patients per each main effects group, we will have 80% power to detect a true effect size of 0.46 standard deviation units. ESIs of this magnitude are between what Cohen describes as a medium (0.5) effect. These are consistent with what we found in our pilot study.

Covariance adjustment for the baseline score of the outcome measure and other important covariates using ANCOVA will increase power, as will the use of all follow-up measures in the mixed-model ANCOVA analysis described above.

Analyses Associated with Open Phase of the Study. We will track the number of patients who receive a dose escalation throughout the study. This information will be summarized for patients who receive methylphenidate to determine the number of patients who received a dose escalation by day 15 and by day 36. We will test if these proportions are significantly different using the McNemar test, which takes into account the matching of the individuals over time.

For the subset of patients who are randomized to receive methylphenidate, we will determine the proportion of patients who are still utilizing the drug at day 15 and at day 36. We will determine if the proportion of patients who use the drug at day 15 differs from the proportion of patients who use the drug at day 36 by using the McNemar test.

For the subset of patients who are randomized to receive methylphenidate, we will determine their global assessment of effectiveness of the treatment at day 15 and at day 36. We will determine if this value decreases over time by subtracting each patient's day 15 value from their day 36 value and using a paired t test to test the null hypothesis that the difference between the two values is zero.

We will summarize side effects for patients receiving methylphenidate and will present the information about side effects that occur before day 15 and that occur between days 15 and 36. We will be able to determine if the number of side effects increase for the two time periods using the sign test. The severity of the side effects will also be summarized, and if there are sufficient numbers to analyze, we will also determine if the number of severe side effects increase between the two time periods using the sign test.

Qualitative Analysis. This study will involve telephone interventions with 106 persons, each called longitudinally at 4 - 6 times, or 424 - 636 calls. In order to understand the essential elements in experience, sufficient numbers of informants must be selected to provide a detailed and clear description of the experience under investigation. The usual way to determine sample size is through saturation, which means researchers conduct interviews until they no longer hear new statements from informants and the data are increasingly redundant. For the purposes of operational and budgetary planning, we will use previous experience and research to project a point at which saturation and a detailed description might be expected. Based on previous research that has obtained detailed description of other experiences, the sample size of this study should be 40 to 60 at each time. This number in fact exceeds the number of interviews and informants used in other research conducted by Cohen and others. However, this will enable the research team to interview sufficient numbers of both genders and members of minority groups to accurately understand themes that vary by ethnicity or gender. This should allow phenomena to be captured in their complexity.

In prior research, this has meant that the themes identified were present in the majority of informants' descriptions. For example, Cohen and Ley (109) interviewed 20 BMT patients who were long-term survivors, Cohen and Sarter (110) interviewed 32 nurses to describe the experience of oncology nursing, and Cohen, Haberman, and Steeves (111) conducted a multi-site study of the meaning of oncology nursing with 76 interviews with 38 nurses. Bondas-Salonen (112) interviewed 40 women about the experience of having their partners present at the birth of their children. Hanna's (113) study of the meaning of health involved 29 informants. Wilson and Morse (114) included data from 48 interviews with 15 husbands of women undergoing chemotherapy. These numbers of informants were sufficient to obtain detailed descriptions of the experiences under study. Analysis of 636 transcripts may well be more than is needed, but the analysis will be used for both to assure that the quality of the intervention does not change over time or differ among the nurses as well as to understand the intervention and patients' experiences. These calls are likely to be far shorter than traditional interviews so while the number may seem inordinately high, the data will be briefer than in prior research so the analysis of this number is feasible.

Morse, Penrod, and Hupcey (115) recently described using qualitative data to identify interventions and evaluate outcomes. While our project differs in many ways from what they describe, the idea that applies to this project is that qualitative data are useful to understand and identify interventions that are appropriate for phenomena that change over time, as do symptoms for persons with advanced cancer. Other strategies they describe as useful have been included here, such as including clinicians on the research team. As they note, this strategy addresses both process and outcome and thus enhances the applicability to complex clinical experiences. These strategies will enhance our ability to use these data to understand what is important in the nurse telephone interventions.

The aim is to balance variability and homogeneity. Limiting the sample to patients from two institutions will make it easier to describe the clinical context in detail. However, the variability of the patients should provide enough heterogeneity to allow a wide exploration of the experience of having this nursing intervention.

Analysis and Interpretation of Qualitative Data. These analyses will help accomplish aim 3: Investigate the additive or synergistic effect of methylphenidate treatment plus nurse telephone follow-up on reduction of fatigue compared to either methylphenidate treatment or nurse telephone follow-up alone.
Analysis will follow the approach based on hermeneutic phenomenological approach, also called the Utrecht School of Phenomenology or simply phenomenological research [116-120]. Cohen and the research team will jointly conduct analysis using a process similar to what they used in prior research. Cohen's prior research has demonstrated the advantages of having a team work together to analyze a large volume of data. As in prior studies, once an understanding of the overall text is obtained, phrases in the text are underlined and tentative theme names are written in the margin of the text. Data are examined line by line and all important phrases are labeled with tentative theme names. An example from previous research is the analysis of the following passage:

> "I got the shingles. I never knew what shingles were, and I didn't know and
> I got so scared. And I come there and they're like, 'Oh, don't worry, that

> usually happens to bone marrow transplants after.' And I said, see, no one told me this. You should have told me because I started stressing out... I just think they should prepare people before they go in, of what is going to happen to you after, and what really a transplant is."

This passage was identified as an exemplar and coded as "information needs." Exemplars are defined as bits of textual data in the language of the informant that captures essential meanings of themes. As this example illustrates, analysis of data includes elements within themes. This passage was included in the theme that was finally labeled "a range of needs for information." Many passages were found in these interviews that dealt with patients' needs for information. Analysis made it clear that there were patients who felt staff would tell them what they needed to know, and that they need not ask any questions. Another group wanted to know as much as possible. They mobilized resources outside the hospital to obtain the information they wanted. And finally, another group had questions and fears and was not always clear about what to ask, how to ask it, or who might provide the information or reassurance they wanted. In addition to this range of needs for information, other themes emerged in the analysis that related to patients' information needs, which were described more fully in Tarzian, Iwata, and Cohen [68].

After exemplars are identified, they will be clustered according to observed similarities into themes for each individual informant. Themes and exemplars will be compared for similarities and differences with each informant, across all informants. Important contextual features, such as ethnicity, and how the experiences vary with these features will be included in the analysis. This analysis will identify patterns and relationships among the various informants and form a coherent picture of the whole. Data will also be analyzed to obtain an understanding of the meaning of symptoms and QOL. The computer program Ethnograph or a similar one will be used to facilitate this thematic analysis.

Central to phenomenological methods is the consideration and understanding of the contextual features that are meaningful to the informants. At the outset of the project it is unclear precisely which features will be most meaningful to the informants. Type of cancer, continuity of care, features of the particular professionals with whom they interact, or ethnic and other socio-demographic differences may be meaningful. We will need to see what the data reveal.

A process of writing and rewriting, which is crucial to phenomenology (119), will be used to move from identification and comparison of themes to a coherent picture of the whole. As the research team gains insight into and a tentative understanding of the meaning of the experience of these patients as conveyed through the exemplars and in the themes, this understanding will be summarized in written memos that will be circulated among the members of the research team. These memos will serve to document the process and drive the transformation of the field text to a coherent text through a reflective process of writing and rewriting. All team members will write these memos about the whole of the data. Cohen will coordinate the logistics of the writing and rewriting process of analysis.

Bias Control: The general rule for bias control in qualitative research, whether it is phenomenological or from another school or method, is to open all decision making to inspection by informants, peers and others who have no special attachment to or interest in the specific results of data analysis. This will be accomplished through the use of several procedures developed by Cohen (121) and by Lincoln and Guba (122).

The first procedure will be the use of the research team and the collaborators as a review panel. This panel will be given interviews and asked to identify tentative themes in the text. Next the panel will be given a sample of exemplars and a description of themes and asked to match the exemplars with a theme. The level of agreement among the panel members will be determined. Significant disagreements will be discussed and analysis refined until consensus is reached. Cohen will coordinate this procedure.

Finally, the procedures outlined above have been designed to create a written record of all the decisions made during the research project and justification for each decision. This record will include E-mail communications among the co-investigators, minutes of team meetings, and minutes of the meetings and conference calls with the co-investigators, Cohen will maintain this record as part of the study archive along with all data and the analytic memos. This decision record in conjunction with the other materials will provide an audit trail to answer any questions about the reasoning or justification of any decisions made during the study.

Triangulation: Linking analysis of qualitative and quantitative data. These techniques will help accomplish aim 3: Investigate the additive or synergistic effect of methylphenidate treatment plus nurse telephone follow-up on reduction of fatigue compared to either methylphenidate treatment or nurse telephone follow-up alone.

Data will be analyzed with appropriate techniques (phenomenological data will be analyzed with phenomenological techniques, and statistical analysis will be conducted on quantitative measures) (123). Data will then be linked in several ways. First, groups will be formed on the basis of scores on the structured measures (e.g., high, moderate, low fatigue). In addition we will develop major qualitative themes or results (e.g., different meanings attached to symptoms) and examine how variation in the qualitative data link to variation in the quantitative date. Matrices will be developed that combine and compare the qualitative and quantitative data groups (124-125). In the quantitative analysis, patient profile plots will be constructed for each of the symptoms, and quality of life to describe the individual patient's patterns of change over time. We will add the major phenomenological themes over time to these profiles to enhance our understanding of the factors associated with various patterns. In addition, we will develop exemplar cases, for example, cases that illustrate different trajectories over time. In these cases the diverse sources of data would provide a more comprehensive understanding of the recovery trajectory. We envision the data linking will serve multiple purposes. These include understanding the meaning of the symptoms and quality of life in more detail than is possible without the qualitative data. Marlene Cohen, our co-investigator, has experience with triangulation and will provide guidance for the processes used to link the qualitative and quantitative data.

7.0 References

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