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Effects of Armodafinil and Cognitive Behavior Therapy for Insomnia on Sleep Continuity and Daytime Sleepiness in Cancer Survivors

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Abstract

Study Objectives—This study involves the analysis of a secondary outcome of a trial examining whether cognitive behavior therapy for insomnia (CBT-I), a wake-promoting medication (armodafinil), or both results in greater improvement in prospectively assessed sleep continuity and daytime sleepiness than a placebo-alone group among a heterogeneous group of cancer survivors. Whether or not armodafinil alone, and/or when combined with CBT-I, affected adherence with CBT-I was evaluated.

Design—This study is a randomized, placebo-controlled, clinical trial.

Setting—This study was conducted at two northeastern academic medical centers.

Participants—Eighty-eight cancer survivors with chronic insomnia were recruited between October 2008 and November 2012. Participants were assigned to one of four conditions: 1) CBT-I

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and placebo (CBTI+P); 2) CBT-I and armodafinil (CBT-I+A); 2) armodafinil alone (ARM); or 4) placebo alone (PLA).

Interventions—CBT-I was delivered in seven weekly individual therapy sessions (three in person, four via telephone). The armodafinil dosage was 50 mg BID.

Measurements and Results—Sleep continuity was measured with daily sleep diaries assessing sleep latency (SL), wake after sleep onset (WASO), and total sleep time (TST). The Epworth Sleepiness Scale (ESS) measured daytime sleepiness. Compared to the PLA group, the CBT+P and CBT+A groups reported a significant reduction in SL with effect sizes of 0.67 and 0.58, respectively. A significant reduction was observed in WASO in the CBT+A group with an effect size of 0.64. An increasing trend of TST was observed in the CBT+P, CBT+A, and PLA groups, but not in the ARM group. No statistically significant reductions in daytime sleepiness (ESS) were observed for any of the groups.

Conclusion—CBT-I alone and in combination with armodafinil caused significant improvement in sleep continuity. The addition of armodafinil did not appear to improve daytime sleepiness or enhance adherence to CBT-I.

Keywords

Cancer; insomnia; cognitive behavior therapy; CBT-I; armodafinil; sleepiness

INTRODUCTION

Early cancer detection and treatment advances have resulted in a substantial increase in the number of individuals who survive cancer. This has brought to the fore the need to ensure the health, wellbeing, and quality of life of more than 13 million cancer survivors.[1] Perhaps the most prominent residual or long-lasting symptoms of cancer are fatigue and insomnia. With respect to the latter, several large-scale epidemiological studies demonstrate that nearly 60% of people treated for cancer experience insomnia.[2,3] Insomnia (sleep continuity disturbance) and daytime sleepiness are especially important consequences of cancer because of their potential to negatively influence physical and psychological well-being and overall quality of life.[4,5] While the high incident rate of insomnia in the context of a cancer diagnosis and treatment is not unexpected, it is often the case that sleep continuity disturbance tends to be unremitting long into remission and recovery from cancer.[3] In these cases, interventions are required for improved sleep.

Presently, the primary indications for chronic insomnia are medical treatment and cognitive behavioral therapy for insomnia (CBT-I).[6,7] Medical treatments include pharmacotherapy with benzodiazepine receptor agonists (BZRAs, e.g., zolpidem/ambien; melatonin agonists, e.g., ramelteon/rozerem; low-dose antidepressants, e.g., doxepin/silenor; and, most recently, an orexin antagonist suvorexant/belsomra). Of these options, the most exhaustively studied medications are the benzodiazepine receptor agonists. These medications produce good effect sizes with respect to sleep continuity,[8,9] and evidence suggests that such effects may be maintained over time with continued use of medications.[10] CBT-I has also been shown to have similar effect sizes with respect to sleep continuity[11,12] and comparable or better effects than BZRA hypnotics.[13,14] Unlike medication, the effects of CBT-I are durable and

extend beyond acute treatment for measured periods of up to 24 months.[15,16] Further, >55% of patients treated with CBT-I reach remission within 6 months of the discontinuation of acute therapy.[17,18] Given these outcomes, it can be argued that CBT-I is the treatment of choice for chronic insomnia (in general), especially for patients who prefer not to use medication. CBT-I appears well suited to cancer survivors with insomnia. To date, eight controlled and four uncontrolled trials of CBT-I have been conducted in cancer patients. A systematic review of these studies concluded that CBT-I is effective in this context with one study showing large effect sizes for sleep latency (SL), wake after sleep onset (WASO), and sleep efficiency (SE).[19]

Despite the evidence that CBT-I is an effective intervention, there remains a significant proportion of individuals whose insomnia does not respond to, or remit after, treatment. Estimates suggest that 32–89% of patients treated with CBT-I (including those with cancer) do not consistently follow treatment recommendations.[20] While the reason for this is unknown, it has been suggested that the transient decrease in total sleep and/or the transient increase in daytime sleepiness that is inherent to CBT-I is simply intolerable for some patients,[21] particularly those with high basal levels of fatigue and sleepiness. Given this possibility, it follows that daytime use of a wakefulness promoting medication should, by itself, decrease daytime sleepiness (and possibly fatigue) and when combined with CBT-I, prevent the “iatrogenic” effects of CBT-I with respect to daytime sleepiness and potentially increase adherence given the reduced consequences of delaying time to bed (TTB) and the practice of stimulus control.[21] These possibilities were evaluated in one study of patients with primary insomnia. In this study, it was found that modafinil (alone or in combination with CBT-I) did not change the outcomes with respect to sleep continuity, but did significantly alter daytime sleepiness and adherence to CBT-I.[21] Further, reducing the negative consequences (side effects) of CBT-I should have a positive effect on adherence. These possibilities have been evaluated in non-cancer patients with primary insomnia. In this context, it was found that modafinil,[22-24] alone or in combination with CBT-I, did not affect sleep continuity but did significantly alter daytime sleepiness and adherence to CBT-I.[21] Our own group also conducted a two-site study in which CBT-I, armodafinil, and the combination (as compared to placebo) were evaluated in cancer survivors with insomnia.[25] It was found that subjective insomnia severity and sleep quality as assessed by the Insomnia Severity Index (ISI) and the Pittsburgh Sleep Quality Index (PSQI) were significantly improved in both CBT-I conditions. In the present analysis, a focused and quantitative evaluation of sleep is undertaken using prospective sampling measures (sleep diaries) to evaluate whether 1) sleep continuity was differently affected by the interventions; 2) armodafinil alone, or in combination with CBT-I, effects sleepiness; and 3) armodafinil in combination with CBT-I affected adherence measures as compared to CBT-I alone (with placebo). An examination of sleep via daily diaries provides a more sensitive measure of sleep continuity disturbance than qualitative measures such as the ISI.

METHODS

Design

The parent study for this analysis was a randomized, placebo-controlled, clinical trial of post-treatment cancer survivors with chronic insomnia. The complete methods of this study have been published elsewhere[25] and will only be briefly summarized here. Eighty-eight cancer survivors were assigned to one of four conditions: 1) CBT-I plus placebo (CBT-I+P; $n = 21$); 2) CBT-I plus armodafinil (CBT-I+A; $n = 22$); 3) armodafinil only (ARM; $n = 22$); or 4) medication placebo only (PLA; $n = 23$). Patients were assessed at the following time points: baseline (2 weeks), during the intervention period (weekly for 7 weeks), and post intervention (2 weeks). The reporting of this trial follows the CONSORT guidelines for reporting randomized trials of behavioral and pharmacological interventions. The institutional review boards of the University of Rochester and the University of Pennsylvania approved the protocol, and patients provided written informed consent. This trial is registered with ClinicalTrials.gov, number NCT01091974.

Inclusion Criteria

Cancer survivors with chronic insomnia in two northeastern cities were screened and recruited between October 2008 and November 2012. No restrictions were placed on cancer type but participants must have been presumed cancer-free at the time of enrollment. Participants must have completed all therapeutic cancer treatments not less than a month prior to study start (continued use of tamoxifen or an aromatase inhibitor was permitted). Participants were required to discontinue any prescribed or over-the-counter medications for sleep for the 11-week study period and have a preferred sleep phase between 7:30 pm and 11:00 am. They also had to endorse problems with insomnia for at least 3 months and state that the insomnia began, or became worse, with the onset of cancer or cancer treatment. Insomnia symptoms were assessed with an online screener and were corroborated with 2 weeks of sleep diaries. Participants were required to have reported SL or WASO problems of >30 min, problem frequency of >3 days per week, and problem chronicity of >1 month). Patients who had ever taken modafinil or armodafinil; had undergone CBT-I therapy; had a history of seizures or severe headaches, or uncontrolled cardiac disease or hypertension; had taken amphetamines within the past 30 days; had a history of substance abuse or meet criteria for current alcohol abuse or dependence; or had sleep apnea, were not eligible.

Measures

Sleep diaries—This instrument provides a night-by-night, self-report measure of sleep continuity and is considered the gold standard for the measurement of insomnia.[26,27] The specific variables captured are TTB, time out of bed (TOB), SL, WASO including early morning awakenings, and total sleep time (TST). In addition, three variables were calculated based on the diary data including time in bed (TIB), TST, and SE. All sleep continuity variables were converted into weekly averages.

Epworth Sleepiness Scale (ESS)—The ESS is a validated and well-established measure of daytime sleepiness.[28] It is a self-administered questionnaire where respondents are asked to rate, on a four-point scale (0–3), their usual chances of dozing off or falling

asleep in eight different situations or activities that most people engage in as part of their daily lives. ESS scores range from 0 to 24. Scores of 0–7 represent normal levels of sleepiness, 8–9 represent average sleepiness, 10–15 excessive sleepiness, and 16–24 pathological sleepiness.

Adherence—Diary values for each sleep continuity variable were aggregated by week. Treatment adherence was evaluated by examining the actual time in bed (ATIB) compared to the prescribed time in bed (PTIB) for each week for the CBT-I+P and CBT-I+A groups. Patients were introduced to sleep restriction at their first CBT-I appointment. ATIB was determined from the TTB and TOB questions on the sleep diary. PTIB was recorded by the therapist for each CBT-I session. For example, if the average baseline TST was 6 h, then the PTIB would be 6 h. An individual was deemed adherent if his/her ATIB was ±30 min of his/her PTIB. Adherence was calculated for each week and coded as yes/no. The number of adherent weeks was divided by the total number of sleep diaries returned to calculate an adherence percentage. We assessed compliance with study medication in two ways: 1) The report of pill use on the sleep diaries and 2) whether the pill slot in the returned foil pack was filled or empty.

Intervention Details

CBT-I combines principles from stimulus control therapy (reducing non-sleep behaviors in the bedroom) and sleep restriction therapy (consolidation of sleep periods) with formal cognitive restructuring (reducing misconceptions about sleep) in order to target hyperarousal, maladaptive behaviors, and negative beliefs, and attitudes associated with insomnia. CBT-I was delivered over the course of seven weekly individual sessions. Sessions 1, 2, and 4 were in person (30–60 min in duration) and sessions 3, 5, 6, and 7 (15–30 min in duration) were by phone. The delivery of CBT-I interventions via telephone is comparable to face-to-face delivery[29] and has been demonstrated to reduce patient burden and increase retention of participants.[30]

Armodafinil is a single isomer formulation of modafinil (R-enantiomer of modafinil). It is indicated for the promotion of wakefulness in several sleep disorders including narcolepsy, sleep apnea syndrome, and shift work disorder. It is available in 50, 150, or 250 mg tablets. Medication was begun with a 50-mg dose of armodafinil in the morning (7–9 am) along with an afternoon (12–2 pm) administration of placebo. After 3 days, active doses of armodafinil were administered both in the morning and afternoon (50 mg each). Twice daily treatment was continued for 40 days and then was followed by 4 days of 50 mg in the morning and a placebo in the afternoon. Patients in the PLA group received a placebo capsule in the morning and afternoon to mimic the dosage times of the ARM group, and all patients received information on sleep hygiene.

Study personnel and patients were blinded regarding medication (armodafinil, placebo) assignment but not CBT-I condition, and participants were not randomized until after the completion of their 2-week baseline period. Participants had the option of completing measures using paper and pen on scannable forms or using an internet data portal. Scannable

data were electronically transferred to an Access database, and data quality was checked by an information analyst.

Statistical Analyses

Sample size calculations were performed for the primary analysis and have been reported previously.[25] ANCOVA (analysis of covariance) was employed on the post-intervention score (average of the 2 post-intervention weeks), controlling for the baseline score. Using appropriate contrasts, the mean post-pre-change was estimated for CBT-I+A versus placebo, CBT-I+P versus placebo, armodafinil versus placebo, and CBT-I+A versus CBT-I+P. We considered 0.0125 as the significance level to control for multiplicity. Analyses were carried out with the intention to treat, although 23 (24%) of the 96 randomized eligible patients did not provide post-intervention data. The missing value patterns were examined through visual inspection and logistic regression of missingness versus treatment arm and demographic characteristics. Examining the reasons for dropout, we found no evidence that the data were not missing at random and therefore assumed a missing at random (MAR) mechanism.[26] We therefore applied multiple imputation (MI) using data from all participants who had baseline data. The MI analyses results were similar to the complete case analyses in which only those patients who provided post-intervention data were included. SAS Version 9.2, SPSS version 19, and R Version were used for the present analyses.

RESULTS

Of the 138 patients who consented to screening, 114 were eligible and 96 were randomized; 88 (77% of eligible patients and 92% of randomized patients) began the intervention, and 73 patients (83% of the 88 patients beginning the intervention) completed the 7-week intervention. No serious related adverse events were reported. Average compliance with the study medication, as determined by the returned study medication cards, was >90% for all study arms and did not differ significantly by group. There were no differences between the treatment groups for any baseline characteristics (Table 1). For specific details regarding subject attrition and details on adverse events, please see our prior publication's CONSORT diagram.[25]

Sleep Continuity

Between Group Effects—Table 2 presents the between-group analyses of treatment condition for the sleep continuity variables. Participants in the CBT-I+A ($p < .001$) and CBT-I+P ($p = 0.003$) groups had significantly shorter SLs than those in the PLA group. No significant differences were observed in SL between the ARM and PLA groups ($p = .17$) or the CBT-I+A and CBT-I+P groups ($p = .60$). For reducing the amount of time spent awake during the night (WASO), the results suggest a trend with subjects in the CBT-I+A group doing slightly better than those in the PLA group ($p = .02$). No other between-group differences were found with respect to WASO. There were no significant between-group differences in TST.

Within-Group Effects—Figure 1 presents the weekly data for SL, WASO, and TST. Table 3 presents these data as between-group differences in sleep continuity variables compared to

PLA. As can be seen in Fig. 1 and Table 3, subjects receiving CBT-I experienced a statistically significant reduction in SL, with or without the addition of armodafinil (−37 min in CBT-I+P, $p < .001$; −26 min in CBT-I+A, $p < .001$). No significant changes in SL in the ARM or PLA groups were observed. CBT-I with or without the addition of armodafinil resulted in comparable changes in time spent awake after sleep onset (−14 min in CBT-I+P, $p < .001$; −17 min in CBT-T+A, $p < .001$). There was no significant reduction in the amount of time spent awake during the night in the ARM or PLA groups.

Daytime Sleepiness

As can be seen in Table 4, participants in the CBT-I+P ($p = 0.02$) and CBT-I+A ($p = 0.03$) groups reported reductions in daytime sleepiness, but this did not reach statistical significance. There was no significant reduction in daytime sleepiness in the ARM or PLA groups. No between-group differences were observed.

Adherence

No significant differences were noted in the overall adherence observed between the patients assigned to CBT-I+A (M = 67.67, SD = 29.79) or CBT-I+P (M = 54.78; SD = 30.73), $t(38) = 1.34$, $p = 0.19$. Figure 2 plots adherence over time for both CBT-I groups. Average adherence with study medication was >90% for all study arms and did not differ significantly by group.

DISCUSSION

This study examined the effect of CBT-I +/-− armodafinil on sleep continuity variables, daytime sleepiness, and adherence to sleep restriction instructions in a heterogeneous group of cancer survivors. The results from this study show that CBT-I (with or without armodafinil when compared to placebo) reduces SL in cancer survivors. Supplementing CBT-I with the wake-promoting medication armodafinil did not differentially influence sleep continuity variables, reduce sleepiness, or increase adherence. CBT-I, with or without armodafinil, decreased SL by ~30 min, reduced time spent awake during the night by ~15 min, increased TST by ~30 min, and decreased daytime sleepiness by an average 1.75 points. These findings correspond to large pre-to-post effect sizes for SL and WASO and a moderate (but not statistically significant) effect size for TST. The findings are consistent with other trials of CBT-I in cancer.[31-33] The lack of effect for TST (during the acute treatment phase) is common to most CBT-I trials and represents the transient effects of sleep restriction (restricting TIB).[13]

Of note, patients in the placebo condition (in the absence of improvement on SL and WASO) also exhibited a trend toward increased TST with an average increase of 52 min of sleep per night. This effect may be ascribable to expectancy or the effects of increasing sleep opportunity (extending TIB) over time. In the case of the former, this is in line with recent studies that demonstrate strong subjective responses to placebos in the treatment of insomnia[34,35] and highlights the importance of patient expectancy on outcomes in medication trials.

There are a number of possible reasons behind the inability of armodafinil to produce an additive effect on sleep continuity variables. First, several well-conducted trials have concluded that CBT-I produces robust clinical improvements in sleep outcomes in cancer survivors,[19] and it may be difficult to improve sleep much beyond these effects, especially in the context of cancer. Alternatively, the standardized dosing protocol might have contributed to the lack of effect. In clinical practice, armodafinil dosing is individualized according to patient report of difficulty with either daytime sleepiness or difficulty staying awake until prescribed bedtime. Potentially, this problem could be resolved with a flexible dosing trial. Another (and related) possibility is that daytime sleepiness and high rates of daytime napping are predictive of treatment intolerance, attrition, and nonadherence. This, in combination, with the relatively low dose of armodafinil may have resulted in the lack of therapeutic effects.

The lack of finding with respect to sleepiness is surprising; there is, however, a precedent for modafinil/armodafinil's lack of effect on fatigue. Several other trials in cancer have shown modafinil (and its enantiomer armodafinil) to be largely ineffective for cancer-related fatigue – a similar yet conceptually different phenomenon from daytime sleepiness.[36-40] Both fatigue and sleepiness have physical and mental weariness as a component feature, but only sleepiness addresses the issue of the individual's ability to stay wake when sleep is unwanted, inappropriate, or dangerous. It is also possible that patients in this trial were not pathologically sleepy (with or without the transient adverse effects of CBT-I). Consistent with this possibility is that the baseline ESS in this study was 8, which is almost identical to ESS scores in adult community samples,[41] thereby indicating the possibility of a floor effect. By contrast, reductions in fatigue and/or sleepiness have been reported for patients with obstructive sleep apnea, ALS, major depressive disorder, and human immunodeficiency virus (HIV).[42-45] Future studies are required to understand the exact nature of sleepiness and fatigue in cancer patients in order to design effective interventions.

The inability to demonstrate an effect of armodafinil on adherence is less surprising, especially given the nonsignificant effects on daytime sleepiness. While adherence to prescribed bed and wake times is an identified mediator of treatment effect,[46] it is possible that our measure of adherence was not sensitive enough to assess the relative benefit (or lack thereof) of armodafinil in patients also receiving CBT-I. This may be true for two reasons: First, our measure of adherence (PTIB) was a global construct that did not allow for the assessment of patient adherence specifically to the prescribed TTB, the time spent out of bed at night, and the prescribed "rise time" (TOB). Thus, it was only possible to assess adherence to reduced TIB and not whether subjects were staying up to the appointed hour, leaving the bedroom when awake, or rising at the appointed hour regardless of the prior night's sleep. A sharper resolution on these factors may have revealed changes in adherence where the global measure did not. Second, measuring adherence as a dichotomous variable may not adequately capture the complexity inherent in adherence to a behavioral intervention. Lastly, while adherence to CBT-I has room for improvement, it is comparable to other behavioral interventions (e.g., physical activity[47] and lymphedema self-care[48]). As such, future efforts may focus on identifying those at risk for poor adherence and providing individual intervention instead of applying these techniques across all participants.

In summary, CBT-I was associated with clinically significant reductions in insomnia symptoms, specifically in SL and WASO in cancer survivors. The addition of armodafinil did not appear to enhance the overall efficacy of CBT-I on sleep continuity or daytime sleepiness. Armodafinil also did not significantly improve patient adherence with TIB prescriptions when administered in conjunction with CBT-I. These findings are consistent with other trials demonstrating that CBT-I causes robust and durable improvement in terms of cancer-related insomnia. Our results also add to a growing body of literature suggesting that armodafinil and/or modafinil are not effective pharmacological interventions for improving sleep and daytime function in cancer survivors. Future efforts should be focused on improving the availability of CBT-I within cancer centers, health networks, and in the community.

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Highlights

- Cognitive behavior therapy for insomnia (CBT-I) is effective but adherence could be improved.
- A wake-promoting medication (armodafinil) may help patients adhere to treatment.
- CBT-I, with or without armodafinil, improves sleep continuity and sleepiness in cancer survivors.
- Armodafinil did not increase adherence to CBT-I recommendations.
- Future efforts should focus on identifying those at risk for poor adherence.

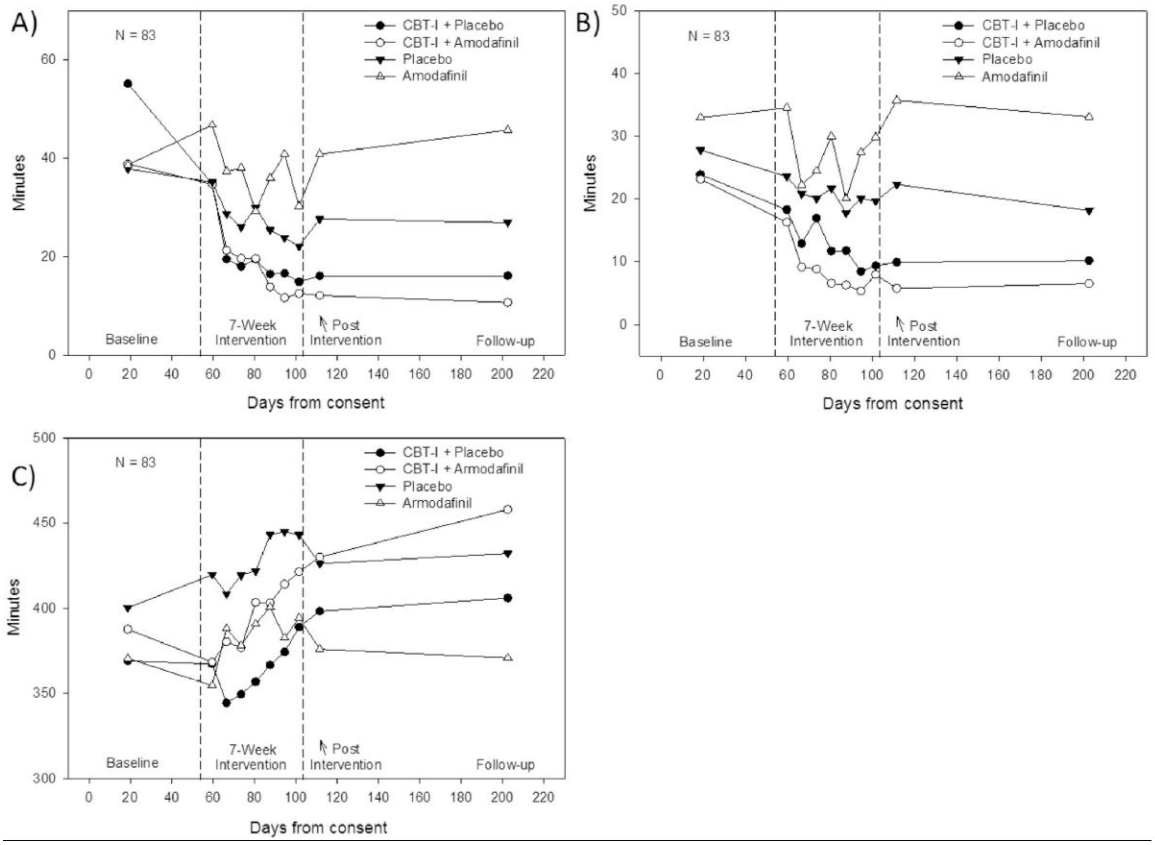
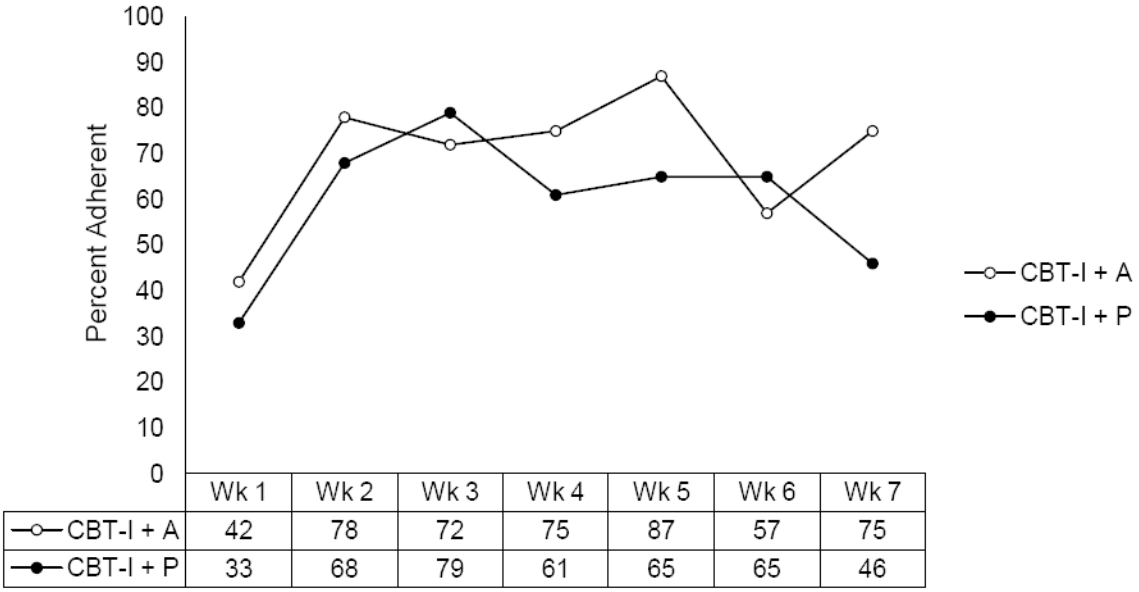


Figure 1.

Effect of treatment arm on sleep latency, wake after sleep onset, and total sleep time.

Refer to Table 3 for within-group change values. A) Sleep Latency; B) Wake after Sleep Onset; C) Total Sleep Time.

Data points for baseline, post-program, and follow-up represent the raw average of 2 weeks. *N* per study arm beginning the intervention, at post intervention and at follow-up includes CBT-I + Placebo, 21, 19, 16; CBT-I + Armodafinil, 22, 17, 16; Placebo, 29, 14, 16; Armodafinil, 21, 14, 15.



	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7
CBT-I + A	42	78	72	75	87	57	75
CBT-I + P	33	68	79	61	65	65	46

Figure 2.

Weekly CBT-I adherence percentages by group.

Note: Adherence was evaluated by examining the actual time in bed compared to the prescribed time in bed for each week. Sleep restriction was initiated in the first session for the CBT-I+P and CBT-I+A groups only. Actual time in bed (ATIB) was determined from the time to bed and time out of bed questions on the sleep diary. Prescribed time in bed (PTIB) was recorded by the therapist for each CBT-I session. An individual was deemed adherent if his/her ATIB was +/-30 min of his/her PTIB. Adherence is relative to sample size.

Table 1

Characteristics of patients beginning intervention by study group

		CBT-I + Placebo *N* = 21	CBT-I + Armodafinil *N* = 22	Placebo *N* = 22	Armodafinil *N* = 23
Age:	Mean (SD)	59 (10.3)	56 (10.2)	52 (11.8)	57 (7.5)
Sex:	Male	3 (14%)	1 (5%)	6 (27%)	1 (4%)
	Female	18 (86%)	21 (95%)	16 (73%)	22 (96%)
Ethnicity:	Non-Hispanic	20 (95%)	21 (95%)	21 (95%)	21 (91%)
	Unknown	1 (5%)	1 (5%)	1 (5%)	2 (9%)
Race:	White	20 (95%)	20 (91%)	18 (82%)	22 (96%)
	African American	1 (5%)	2 (9%)	3 (14%)	1 (4%)
	Unknown			1 (5%)	
Education:	Beyond high school	18 (86%)	18 (86%)	20 (91%)	23 (100%)
	High school or less	3 (14%)	3 (14%)	2 (9%)	
Married	Yes	12 (57%)	15 (68%)	16 (73%)	12 (52%)
Time from last cancer Tx to intervention:	Mean (days)	1,625	1,647	654	1363
	Minimum	136	48	112	104
	Maximum	7,071	10,034	1957	6115
Type of cancer	Breast	15 (71%)	16 (73%)	13 (59%)	16 (70%)
	Other	6 (29%)	6 (27%)	9 (41%)	7 (30%)
Type of cancer treatment	Chemotherapy	16 (76%)	17 (77%)	19 (84%)	21 (92%)
	Radiotherapy	17 (81%)	17 (77%)	16 (73%)	16 (70%)
Insomnia at time of consent [1]	Mean (SD)	15.5 (4.7)	15.0 (5.5)	14.0 (5.1)	14.7 (4.5)

[1] From Insomnia Severity Index

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Table 2

Between group changes in sleep continuity variables compared to placebo.

	Estimate	SE	Lower 95% CI	Upper 95% CI	*p*-value	Effect Size
Sleep latency						
CBT-I + Placebo vs. Placebo	-18.62	5.25	-29.14	-8.10	<0.001 **	-0.67
CBT-I + Armodafinil vs. Placebo	-16.16	5.27	-26.73	-5.59	0.003 **	-0.58
Armodafinil vs. Placebo	7.98	5.68	-3.45	19.41	0.17	0.29
CBT-I + Armodafinil vs. CBT-I + Placebo	2.46	4.67	-6.70	11.61	0.60	0.09
Wake after sleep onset						
CBT-I + Placebo vs. Placebo	-10.00	5.50	-20.96	0.96	0.07	-0.48
CBT-I + Armodafinil vs. Placebo	-13.14	5.59	-24.27	-2.01	0.02	-0.64
Armodafinil vs. Placebo	10.23	7.56	-5.05	25.51	0.18	0.50
CBT-I + Armodafinil vs. CBT-I + Placebo	-3.14	5.16	-13.24	6.97	0.54	-0.15
Total sleep time						
CBT-I + Placebo vs. Placebo	-28.69	19.43	-67.65	10.27	0.15	-0.39
CBT-I + Armodafinil vs. Placebo	-16.00	20.36	-56.93	24.93	0.44	-0.22
Armodafinil vs. Placebo	-51.30	21.80	-95.24	-7.37	0.02	-0.69
CBT-I + Armodafinil vs. CBT-I + Placebo	12.69	17.68	-21.97	47.35	0.47	0.17

* $P < 0.01$,

** $P < 0.001$ A significance level of 0.0125 was used to adjust for multiple comparisons. (Asterisks denote improvements compared to placebo for between group analyses.); All analyses used multiple imputation; *P*-values for between group analyses are from ANCOVA controlling for values at time of consent; Effect size is Cohen's D.

Table 3

Within group changes in sleep continuity variables from pre-to post-intervention

	Pre (SE)	Post (SE)	Post-Pre (SE)	Lower 95% CI for Mean	Upper 95% CI for Mean	*p*-value	Effect Size
Sleep latency							
CBT-I + Placebo	52.89 (6.14)	15.47 (2.81)	-37.42 (5.31)	-48.48	-26.36	<0.001 **	-1.24
CBT-I + Armodafinil	39.34 (6.20)	13.52 (2.84)	-25.82 (5.29)	-36.87	-14.76	<0.001 **	-0.87
Armodafinil	37.63 (4.26)	37.11 (5.08)	-0.52 (4.06)	-9.30	8.25	0.90	-0.03
Placebo	41.40 (6.51)	30.36 (5.16)	-11.04 (6.59)	-24.90	2.82	0.11	-0.38
Wake after sleep onset							
CBT-I + Placebo	23.25 (3.15)	9.30 (2.36)	-13.95 (2.88)	-19.97	-7.93	0.001 **	-0.91
CBT-I + Armodafinil	22.59 (3.01)	5.83 (1.73)	-16.76 (3.12)	-23.30	-10.23	<0.001 **	-1.16
Armodafinil	32.95 (5.17)	34.41 (8.66)	1.45 (8.18)	-16.24	19.15	0.86	0.06
Placebo	29.56 (5.77)	22.47 (4.22)	-7.09 (3.89)	-15.27	1.08	0.09	-0.27
Total sleep time							
CBT-I + Placebo	378.12 (17.29)	405.45 (16.94)	27.32 (9.88)	6.48	48.17	0.01	0.33
CBT-I + Armodafinil	395.47 (16.14)	430.75 (16.07)	35.29 (13.06)	7.38	63.19	0.02	0.46
Armodafinil	371.45 (13.72)	377.98 (19.56)	6.53 (15.74)	-27.73	40.79	0.69	0.10
Placebo	394.17 (16.31)	445.81 (19.80)	51.64 (19.00)	11.10	92.18	0.02	0.71

* $P < 0.01$,

** $P < 0.001$;

A significance level of 0.0125 was used to adjust for multiple comparisons. (Asterisks denote improvements from pre-intervention for within group analyses.); All analyses used multiple imputation; Effect size is Cohen's *D*.

Table 4

Comparison of Epworth Sleepiness Scale at post-intervention by study conditions, as well as within group changes from pre-to post-intervention

Epworth Sleepiness Scale	Estimate	SE	Lower 95% CI	Upper 95% CI	*p*-value	Effect Size
Between Group						
CBT-I + Placebo vs. Placebo	-0.42	1.12	-2.64	1.81	0.71	-0.09
CBT-I + Armodafinil vs. Placebo	-0.67	1.12	-2.90	1.56	0.55	-0.15
Armodafinil vs. Placebo	-0.31	1.36	-3.04	2.42	0.82	-0.07
CBT-I + Armodafinil vs. CBT-I + Placebo	-0.26	1.12	-2.44	1.93	0.82	-0.06
	Post-Pre	**SE**	**Lower 95% CI**	**Upper 95% CI**	***p*-value**	**Effect Size**
Within Group						
CBT-I + Placebo	-1.91	0.73	-3.47	-0.35	0.02	-0.51
CBT-I + Armodafinil	-1.57	0.64	-2.93	-0.21	0.03	-0.07
Armodafinil	-1.71	1.29	-4.51	1.10	0.21	-0.47
Placebo	-1.31	0.87	-3.14	0.53	0.15	-0.24

*$P < 0.01$,

**$P < 0.001$;

A significance level of 0.0125 was used to adjust for multiple comparisons. (Asterisks denote improvements compared to placebo for between group analyses and from pre-intervention for within group analyses and improvements compared to placebo for between group analyses.); All analyses used multiple imputation; *P*-values for between group analyses are from ANCOVA controlling for values at time of consent; Effect size is Cohen's *D*.