HHS Public Access

Author manuscript

Support Care Cancer. Author manuscript; available in PMC 2017 March 01.

Published in final edited form as:

Support Care Cancer. 2016 March ; 24(3): 1339–1347. doi:10.1007/s00520-015-2903-6.

Buspirone for Management of Dyspnea in Cancer Patients Receiving Chemotherapy: A Randomized Placebo-Controlled URCC CCOP Study

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Abstract

Purpose—Cancer-related dyspnea is a common, distressing, and difficult to manage symptom in cancer patients, resulting in diminished quality of life and poor prognosis. Buspirone, a nonbenzodiazepine anxiolytic which does not suppress respiration and has proven efficacy in the treatment of generalized anxiety disorder, has been suggested to relieve the sensation of dyspnea

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Data contained in this manuscript was presented at the ASCO annual meeting in 2011.

Conflict of interest: The authors declare that they have no conflict of interest. The authors have full control of all primary data and agree to allow the journal to review their data if requested.

in patients with COPD. The main objective of our study was to evaluate whether buspirone alleviates dyspnea in cancer patients.

Methods—We report on a randomized, placebo-controlled trial of 432 patients (mean age 64, female 51%, lung cancer 62%) from 16 participating CCOP sites with grade 2 or higher dyspnea, as assessed by the Modified Medical Research Council Dyspnea Scale. Dyspnea was assessed by the Oxygen Cost Diagram (OCD; higher scores are better) and anxiety by the state subscale of the State-Trait Anxiety Inventory (STAI-S; lower scores are better) at baseline and after the 4-week intervention (post-intervention).

Results—Mean scores from baseline to post-intervention for buspirone were (OCD: 8.7 to 9.0; STAIS: 40.5 to 40.1) and for placebo were (OCD: 8.4 to 9.3; STAI-S: 40.9 to 38.6) with raw improvements over time on both measures being greater in the placebo group. ANCOVA controlling for baseline scores showed no statistically significant difference between groups for OCD (P=0.052) or STAI-S (P=0.062).

Conclusion—Buspirone did not result in significant improvement in dyspnea or anxiety in cancer patients. Thus, buspirone should not be recommended as a pharmacological option for dyspnea in cancer patients.

Keywords

Cancer; Dyspnea; Anxiety; Buspirone

Introduction

Cancer-related dyspnea is a common and distressing side effect in patients with cancer, whether or not actual lung involvement is present. Dyspnea is a term for the sensation of breathlessness and is defined as a subjective experience of breathing discomfort felt by an individual. Though the underlying pathophysiology is not well understood [1,2], it is known that the symptoms of dyspnea can derive from interactions between multiple different physiological (e.g. physical deconditioning), psychological (e.g. anticipatory anxiety), social (e.g. the unavailability of support) and environmental factors (e.g. cold or hot temperatures) [3]. Dyspnea can also induce secondary physiological and behavioral responses such as increased heart rate, panic symptoms, and avoidance of certain activities [3]. Dyspnea increases in frequency and severity during the course of the disease [4], with prevalence rates ranging from 15-55.5% at diagnosis and 18-79% during the last week of life [5]. While dyspnea is most commonly seen in patients with lung cancer or metastases to the lung, it is also a significant problem in other primary cancer sites [6]. Dyspnea in cancer patients interferes with activities of daily life and may contribute to poorer physical, social and mental well-being, resulting in diminished quality of life (QOL) [7] and poor prognosis [8].

Despite the high prevalence of dyspnea, it remains one of the most refractory and poorly controlled symptoms among cancer patients with traditional pharmacological interventions often being ineffective [1,2]. The causes of dyspnea in patients with cancer can be broken down into direct or indirect. Direct causes of dyspnea are generally tumor-related (e.g., pulmonary mass, bronchial obstruction, pleural effusion), but patients with these conditions may still remain dyspneic even after maximal curative treatment of their tumor and may

benefit from additional symptomatic treatment for dyspnea [9,10]. The indirect causes of dyspnea generally include treatment-related side effects (e.g., chemotherapy-related anemia, pulmonary radiation-related pneumonitis/fibrosis, shortness of breath after surgical resection of part of the lung); comorbid conditions (e.g., COPD, asthma); and psychological factors (e.g., anxiety and depression) [10]. Although there may be medical interventions indicated for treatment of these conditions, further symptomatic treatment may be required to palliate the dyspnea.

Opioids are considered the drug of choice for the pharmacological palliation of refractory dyspnea [11-13]; however, they are associated with side effects (nausea, constipation, drowsiness, and possible respiratory depression) [14]. Evidence on long-term efficacy of opioids is limited and conflicting [15]. Considering that dyspnea has been identified as a cause of anxiety, and anxiety exacerbates dyspnea [16], it has been suggested that strategies to treat anxiety may be helpful in alleviating dyspnea and improving QOL [17]. Benzodiazepines are widely used and recommended as 2nd or 3rd line pharmacological management or as adjuvant therapy for dyspnea, but there is also conflicting evidence regarding their treatment effectiveness [18,19]. Moreover, benzodiazepines can result in adverse effects of sedation, impaired cognition, and respiratory distress [20]. Considering the potential issues with the use of opioids and benzodiazepines, there is a clear need to investigate other treatment options.

Buspirone is a non-benzodiazepine azapirone serotonergic anxiolytic drug, and does not have a significant sedative effect or suppress respiration [21,22]. It has proven efficacy and is considered a common second-line drug in the short-term treatment of generalized anxiety disorder (GAD) [23]. It is generally well tolerated and does not exert anticonvulsant, sedative, myorelaxant or extrapyramidal side-effects nor appear to cause tolerance or withdrawal reactions [21,24]. Buspirone does not have any direct effects on actual dyspnea but is thought to indirectly decrease the sensation of dyspnea by reducing anxiety [21]. There are a number of possible ways by which buspirone may alleviate the dyspnea sensation. First, it may reduce the degree of anxiety experienced by a patient and hence the degree of breathlessness; second, it may reduce the perception of dyspnea by reducing the perceptual responses or its interpretation in the central nervous system; and lastly, buspirone may alleviate the dyspnea sensation by direct local action on peripheral neural receptors in small airways.

The present phase II trial was designed to assess the efficacy of buspirone in decreasing the sensation of dyspnea in patients with all types of cancer. We hypothesized that buspirone intervention would be more effective than placebo in alleviating dyspnea.

Methods

Study design and patients

This study was a multicenter, randomized, double-blind, placebo-controlled clinical trial. The University of Rochester Cancer Center Community Clinical Oncology Program (URCC CCOP) recruited patients from 16 geographically unique private-practice oncology groups in the USA from November 2002 to January 2010. Eligible patients were outpatients with

any cancer diagnosis, receiving chemotherapy and having a screening score of grade 2 or higher within the past 5 days on the Modified Medical Research Council Dyspnea Scale (MMRCDS), which is a widely used and validated screening tool to identify a sufficiently dyspneic population [25]. This was defined as a positive answer to one or more of the following questions: “Do you have to walk slower than people of the same age on the level because of breathlessness, or have to stop for breath when walking at your own pace on the level?” (grade 2); “Do you have to stop for breath after walking about 100 yards or after a few minutes on the level?” (grade 3); and “Are you too breathless to leave the house or breathless when dressing or undressing?” (grade 4). A score of grade 2 or greater on the MMRCDS corresponds to moderate to severe disability due to dyspnea and indicates shortness of breath with minimal activity [26]. Other eligibility criteria were that participants must be at least 18 years of age, have adequate renal, hepatic and cardiac function, as determined by the treating oncologist. Patients with pleural effusions were eligible if the effusion had been drained or treated with sclerotherapy or if the effusion did not require drainage. Anemic patients were eligible if their Hgb at study entry was greater than 8gm/dl and they had not been transfused in the 15 days prior to study entry. Participants who were taking monoamine oxidase inhibitors (MAOIs), or had taken any such drugs within the past 14 days, or who had a history of mania or seizures, or an unstable medical or psychiatric illness, or had previous hypersensitivity reaction to buspirone were not eligible.

The institutional review board of the University of Rochester and each participating site approved the protocol. Written informed consent was obtained from each patient before enrollment. This trial is registered with ClinicalTrials.gov, number NCT00053846.

Randomization and blinding

Eligible patients were randomized using a computer-generated random numbers table to one of the two treatment groups (buspirone, placebo). Randomization was stratified by study site and carried out centrally via a secure internet connection. All study personnel and patients were blinded regarding study medication assignment.

Procedures and assessments

Treatment with oral buspirone or placebo was started on Day 7 of any cycle of chemotherapy and continued for 28 days. Patients took buspirone or placebo on a fixed-dose titration schedule, starting with one capsule daily (10mg) at bedtime for 3 days and then increasing to two capsules daily, in the morning and at bedtime, for the next 25 days of the study period. Treatment was discontinued after day 28. The medication and dosing schedule for the two treatment groups are shown in Table 1. Patients were instructed not to use alcohol or take any medications not previously prescribed by their treating physician during the study period. On enrollment, patients completed on-study questionnaires providing demographic and clinical information, and the MMRCDS. Baseline assessments were completed prior to starting the study medication and within days 5-7 of the current cycle of chemotherapy. Follow-up (i.e., post-intervention) assessments were done 28 days after starting the study medication.

Primary Outcome—The Oxygen Cost Diagram (OCD) was used to evaluate dyspnea on exertion and activities of daily living, as OCD provides a measurement of dyspnea pertaining to activities of daily life. The OCD is a visual analogue scale for quantifying a patient's evaluation of tolerance for exertion, which corresponds to oxygen requirements at different activity levels ("brisk walking uphill," "medium walking uphill," "brisk walking on the level," "slow walking uphill," "heavy shopping," "medium walking," "bed making," "light shopping," "washing yourself," "slow walking on the level," "standing," "sitting," and "sleeping"). Scores range from 2 (i.e., even sleeping induces dyspnea) to 14 (i.e., unable to walk briskly uphill). Higher scores indicate fewer limitations due to dyspnea. The OCD is correlated significantly with other measures of dyspnea including the Baseline Dyspnea Index and the Medical Research Council scale in participants with diverse cardiopulmonary diseases of variable physiologic severity [25]. Further, the OCD is more sensitive to change than the Medical Research Council scale [27].

Secondary Outcome—The State subscale of the validated Spielberger State-Trait Anxiety Inventory (STAI-S) was used to evaluate anxiety experienced at that particular moment, as it is among the most extensively researched and widely used validated measures of general anxiety and has been extensively used to assess anxiety in cancer patients [28]. State anxiety is conceptualized as a transitory emotional state or condition that is characterized by subjective, consciously perceived feelings of tension and apprehension and heightened autonomic nervous system activity [29]. The measure consists of 20 items with four-point scales (not at all, somewhat, moderate, and very much) [28]. The total score ranges from 20 to 80, with higher scores indicating higher anxiety. The internal consistency of its sub-scales is high. Reliability, construct validity, and utility of the scales have been demonstrated in many different populations including oncology patients with test–retest and α-reliability coefficients ranging from 0.83 to 0.92) [28]. Spielberger's recommended cut point of 39-40 on the STAI-S scale has been suggested to detect clinically significant anxiety symptoms.

Participants completed measures using paper and pen on scannable forms and data were electronically transferred to an Access database. The data quality was checked by an information analyst. All adverse events were categorized by using National Cancer Institute Common Toxicity Criteria for Adverse Events, version 3.0.

Statistical Analyses

Our target accrual in the original protocol was 376 participants. We assumed 20% attrition rate and projected the resulting 300 participants (150 per arm) would have 90% power to detect a difference in OCD mean post-pre change scores between arms of 7.2 units at the 0.05 significance level. Final accrual was 432 randomized subjects.

Descriptive statistics were performed for demographic characteristics, clinical variables, and patient reported dyspnea and anxiety. For the primary analysis, ANCOVA was employed on the follow-up OCD score (post), with Arm (i.e., treatment group) as the factor, controlling for the baseline OCD score (pre). Using appropriate contrasts, the mean post-pre change was

estimated for buspirone vs. placebo. Since the randomization was stratified by sites, we first confirmed that there were no mean differences between sites.

All analyses were performed on an intention to treat basis, although 68 (18%) of the 379 patients, who completed baseline assessment, 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. We found no evidence the data were not missing at random and therefore assumed a Missing at Random (MAR) mechanism [30]. Multiple Imputation (MI) was used for estimation and testing of the ANCOVA model parameters. The MI results were similar to the complete case analyses in which only those patients who provided post-intervention data were included. Both sets of results are provided in Table 3, but for space reasons, we provide only the complete case analyses elsewhere in the manuscript. We used SAS Version 9.2, SPSS version 19, and R Version 3.2 (using the MICE Version 2.2 package [31] for MI) for analyses as appropriate.

Results

432 patients were consented and randomized; 379 (88%) completed the baseline assessment and 311 (72%) completed the 28-day intervention and provided follow-up data (Figure 1). Completion rates were very similar between the two treatment groups. Probably, possibly or definitely related adverse events (AEs) were similar between the two treatment conditions with two grade 1 and five grade 2 AEs in the buspirone group and four grade 2 and two grade 3 events in the placebo group. Baseline characteristics by treatment group are shown in Table 2. In the buspirone group at baseline, the mean age (SD) was 62.9 (10.3) years, 54% were female, 61% had lung cancer, 89% were white, 97% were non-Hispanic, and 36% had history of COPD. For the placebo group at baseline, the mean age (SD) was 64.0 (9.4) years, 50% were female, 62% had lung cancer, 89% were white, 98% were non-Hispanic, and 36% had history of COPD. There were no statistically significant differences at the 0.05 significance level for any baseline characteristics between the two treatment groups.

Mean baseline dyspnea severity, as assessed by the OCD score, for buspirone and placebo groups were 8.7 and 8.4, respectively; while mean post-intervention dyspnea score for buspirone and placebo groups were 9.0 and 9.3, respectively (Figure 2a). For the complete case analyses for dyspnea, ANCOVA while controlling for baseline values showed no statistically significant difference between buspirone and placebo groups (P=0.052) (Table 3). Our findings on the secondary outcome of anxiety, as assessed by the STAI-S score, mirrored the findings with the dyspnea i.e., the complete case ANCOVA for anxiety, while controlling for baseline values, showed no statistically significant difference between the buspirone and placebo groups (P=0.062) (Table 3). Mean baseline anxiety scores for the buspirone and placebo groups were 40.5 and 40.9, respectively, indicating mild anxiety levels for both the groups; while mean post-intervention anxiety scores for the buspirone and placebo groups were 40.1 and 38.6, respectively (Figure 2b). In addition, there was only a weak inverse correlation between the mean post-pre dyspnea change scores and concurrent anxiety change scores (R=-0.138; P=0.015).

Discussion

In the present study, the administration of buspirone, 20 mg daily, did not lead to a significant improvement in dyspnea among cancer patients receiving chemotherapy when compared to placebo. Further, there was no significant benefit of buspirone on anxiety compared to placebo. The findings in our study are consistent with the findings of Singh et al. [32], where buspirone did not improve anxiety, dyspnea or exercise tolerance following a 6-week administration period of doses ranging 30– 60 mg daily but were contrary to that of Argyropoulou and colleagues [33]. These latter researchers found significant reductions in anxiety and dyspnea and an increase in exercise tolerance after the completion of a 14-day administration period of buspirone (20 mg daily). We note that both these studies were only a few weeks long, randomized, placebo-controlled, crossover trials with small number of subjects (n=11 and n=16) having stable COPD. A 2010 Cochrane review found no evidence for the use of benzodiazepines to relieve breathlessness in advanced cancer patients [19]. Similarly, we found no evidence for relief of breathlessness with the use of buspirone, an alternate anxiolytic drug, despite an adequately powered sample and a double blinded placebo controlled study design. The study we report herein is the first study to examine the effect of buspirone on dyspnea and anxiety in cancer patients undergoing chemotherapy.

There are several possible explanations for the lack of beneficial response in the present study. First, it is possible that the dose of buspirone may have been too low. Generally, the initiation dosage of buspirone is recommended to be 10–15 mg daily while the target therapeutic or the maintenance dosage is 15–30 mg [34], with 30 mg daily being the recommended dose in patients with GAD [35]. For our study, we chose 20 mg daily, which is in the mid-range of the recommended dosage schedule. Previous studies have shown that mean doses of 18 mg [36] and 23 mg [37] have been effective in alleviating anxiety without increased adverse effects. Moreover, in the study by Singh et al., the administration of 60 mg buspirone was not more effective than lower doses and patients receiving higher doses reported increased side effects of buspirone [32]. Second, perhaps the effect of buspirone was weakened by a BID (twice daily) dosing schedule rather than three times a day (TID). Considering that buspirone has relatively short half-life of approximately 2 to 11 hours [38], it is typically recommended that the initiation and maintenance dose be given TID [34]. However, Sramek et al. showed that there was no difference in the efficacy or safety for buspirone administered as a BID or TID regimen in patients with GAD and both regimens significantly improved anxiety [39]. Furthermore, a BID regimen is more convenient for the patients which could enhance patient compliance.

A third potential explanation for our null finding is that the drug may not have been given long enough to reach full therapeutic levels and demonstrate a significant clinical effect. Previous research in patients with GAD treated with buspirone showed an acceptable decrease in anxiety in about 2 weeks [23]. Other studies have shown a definite alleviation of anxiety after patients had received buspirone for 3 weeks [36,37,40]. In our study, all the patients received the drug for 4 weeks making it unlikely that the patients did not receive the drug long enough.

Fourth, while buspirone has been shown to effectively target generalized anxiety, it may not have been specific enough to target anxiety directly relating to breathing and breathlessness (dyspnea specific anxiety). Besides, the contribution of general anxiety to dyspnea as well as the causal relationship and the direction of influence is not known [2]. Moreover, we found only a weak association between dyspnea and anxiety change scores, which may further explain the lack of effect of buspirone on dyspnea. Lastly, though our patient population had moderate to severe disability due to dyspnea, they only had mild anxiety with an average STAI-S score less than 41, which may have created a floor effect. While the commonly used level to detect clinically significant anxiety symptoms on the STAI-S is 39-40 [41,42], some studies have even suggested a higher cut-off score of 54-55 for older adults [43] and in our study, the mean age for buspirone and placebo groups was 62.9 and 64, respectively. Using a higher cut-off score of 54-55 for older adults would mean that our patient population had no clinically significant anxiety and hence, may further explain the lack of response to buspirone therapy.

The main strengths of this study include the large sample size in a multicenter setting, double-blinded treatment, and the heterogeneity of the sample as studies have shown that dyspnea is also reported for other cancer types besides lung cancer [6]. However, two weaknesses of this study must be considered. First, the OCD has not been validated in this setting and may not have been the best measure of dyspnea for this study. While the OCD is able to distinguish different levels of disease severity [44], and it has been significantly correlated with both the six minute walk test [27] and arterial blood gas abnormalities [45], some have found that it had poor capacity to detect changes in patient functioning over time [44]. This latter failure might have been due to floor or ceiling effects and that factor could also be at play in the present study. Second, compliance with therapy was not measured for this study, and lack of compliance in one or both study arms could have affected the results of our study.

Conclusion

Dyspnea is a prevalent, distressing, and often intractable symptom for cancer patients. There remains a paucity of successful pathophysiological interventions that modify dyspnea sensation for cancer patients. Thus, pharmacologic and nonpharmacologic interventions that alter perception are of interest. Our study, however, did not demonstrate that dyspnea in cancer patients was significantly alleviated by the administration of buspirone nor was anxiety. The data in this study supports the conclusion that buspirone should not be recommended as a pharmacological option for dyspnea in cancer patients.

Acknowledgments

The authors would like to thank the clinicians, patients, clinical staff and data managers who made this study possible.

Funding: This study was funded by the NCI grants U10 CA37420 and R25CA10618.

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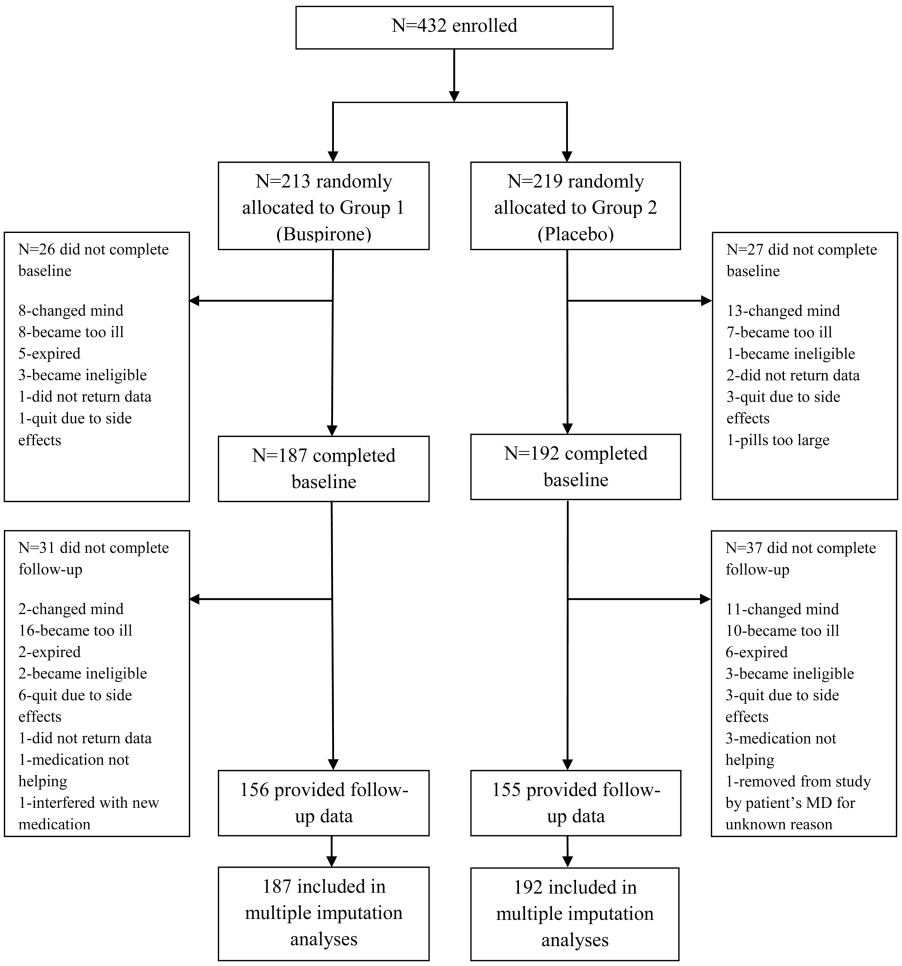

Figure 1.
Consort diagram for primary outcome.

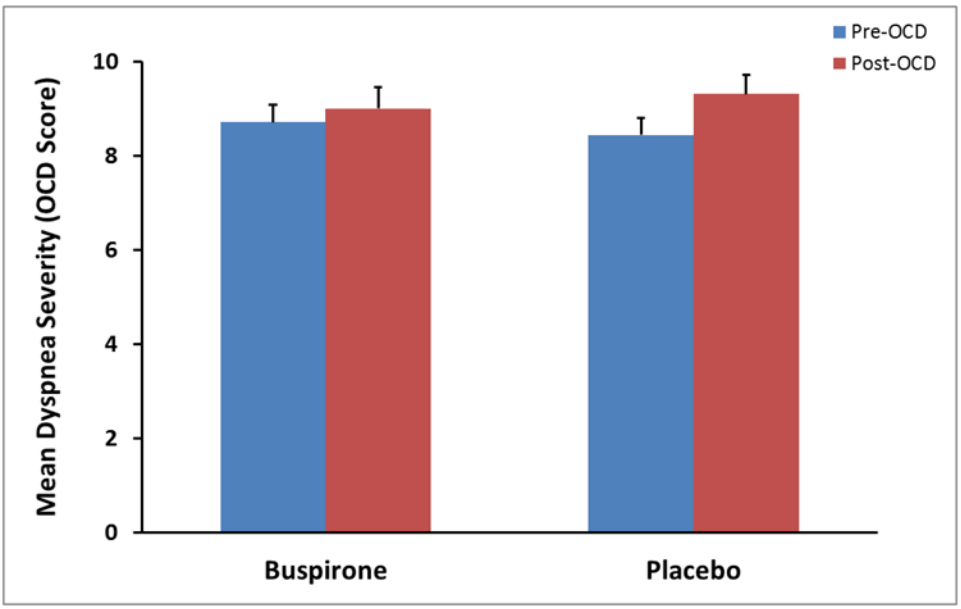

Figure 2a.

Mean severity of dyspnea as assessed by the Oxygen Cost Diagram. Vertical bars are upper limit of 95% confidence intervals (CI). Higher scores indicate fewer limitations due to dyspnea.

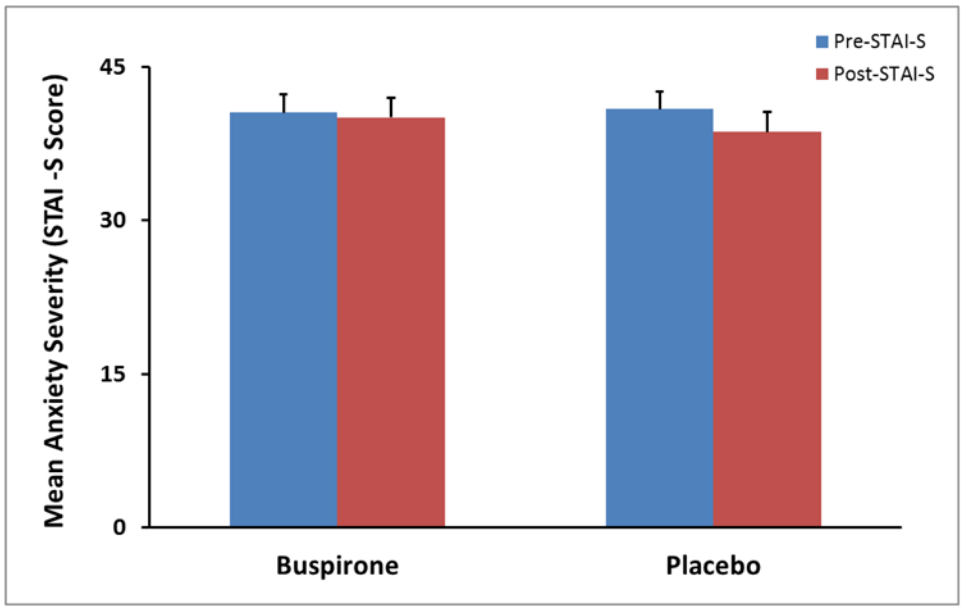

Figure 2b.

Mean severity of anxiety as assessed by the State subscale of the Spielberger State-Trait Anxiety Inventory. Vertical bars are upper limit of 95% confidence intervals (CI). Lower scores indicate less anxiety.

Table 1

28-Day intervention by study arm

	Group 1 **Buspirone**	**Group 2** **Placebo**
Days 1-3	Buspirone – 10 mg p.o. bedtime	Placebo capsule – bedtime[a]
Days 4-28	Buspirone – 10 mg morning and 10 mg bedtime	Placebo capsule – morning and bedtime[a]

[a]Placebo matched to buspirone 10 mg.

Table 2
Baseline characteristics of patients by treatment group

		Drug N = 187	Placebo N = 192
Age:	Mean (SD)	62.9 (10.3)	64.0 (9.4)
Sex:	Male	87 (46.5%)	97 (50.5%)
	Female	100 (53.5%)	95 (49.5%)
Ethnicity:	Non-Hispanic	181 (96.8%)	189 (98.4%)
	Hispanic	----------	2 (1.0%)
	Unknown	6 (3.2%)	1 (0.5%)
Race:	White	166 (88.8%)	171 (89.1%)
	African American	19 (10.2%)	20 (10.4%)
	Other	2 (1.0%)	1 (0.5%)
Education:	Beyond high school	76 (40.6%)	78 (40.6%)
	High school or less	111 (59.4%)	114 (59.4%)
Married		127 (67.9%)	126 (65.6%)
Time from Dx	Mean (years)	2.08	2.30
Type of cancer	Lung	114 (61%)	118 (61.5%)
	Breast	25 (13.4%)	627 (14.1%)
	Gastrointestinal	18 (9.6%)	17 (8.9%)
	Other	30 (16.0%)	30 (15.6%)
Cancer stage	1	10 (5.3%)	12 (6.3%)
	2	17 (9.1%)	18 (9.4%)
	3	49 (26.2%)	53 (27.6%)
	4	103 (55.1%)	102 (53.1%)
	Unknown	8 (4.3%)	7 (3.6%)
History of COPD	Yes	28 (36.4%)	69 (35.9)
Oxygen Cost Diagram at baseline	Mean (SD)	8.7 (2.6)	8.4 (2.6)
[1] MMRCDS grade at baseline	0	4 (2.1%)	2 (1.0%)
	1	21 (11.2%)	23 (12.0%)
	2	77 (41.2%)	80 (41.7%)
	3	61 (32.6%)	54 (28.1%)
	4	22 (11.8%)	32(16.7%)

[1] Modified Medical Research Council Dyspnea Scale (MMRCDS). Note: Patients were consented based upon the MMRCDS screening measure given 5-14 days prior to the MMRCDS baseline measure.

Table 3

Comparison of dyspnea (OCD) and anxiety (STAI-S) at post-intervention by study conditions.

	Estimate	Std. Err.	LCB (95)	UCB (95)	P Value[a]
Dyspnea (OCD)[b]					
Buspirone vs. Placebo:					
Complete case	-0.52	0.27	-1.045	0.005	0.052
Multiple imputation	-0.48	0.27	-1.020	0.058	0.080
Anxiety (STAI-S)[c]					
Buspirone vs. Placebo:					
Complete case	1.83	0.98	-0.092	3.746	0.062
Multiple imputation	1.74	1.06	-0.336	3.823	0.100

[a] P-values denote improvements compared to placebo from comparison by ANCOVA controlling for baselines values;

[b] Oxygen-cost Diagram (OCD);

[c] State subscale of the Spielberger State-Trait Anxiety Inventory (STAI-S). Analyses are presented as both complete case and multiple imputation because of frequent missing data. Estimates and associated statistics refer to differences between groups in mean change from baseline. LCB (95) and UCB (95) are the lower and upper 95% confidence intervals, respectively.