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A Double Blind, Randomized Controlled Clinical Trial Comparing Eicosapentaenoic Acid (EPA) versus Docosahexaenoic Acid (DHA) for Major Depressive Disorder

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Abstract

Importance: The efficacy of omega-3 fatty acids as monotherapy for treatment of major depressive disorder (MDD) remains uncertain.

Objective: To assess the efficacy and safety of two omega-3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), as monotherapy for MDD. We hypothesized that EPA and DHA would demonstrate superiority [KB1]efficacy when compared to placebo.

Design: Eight-week, double-blind, placebo-controlled randomized clinical trial; recruitment from 05/18/06 to 06/30/11.

Setting: Two academic centers, one in the Boston area and the other in the Los Angeles area.

Participants: Random sample, 389 adults recruited through advertisements and referrals, screened for DSM-IV MDD; 196 subjects (53% female; mean age 44.7 ± 13.4 years) meeting criteria for MDD and having a baseline 17-item Hamilton Depression Rating Scale (HAM-D-17) score ≥ 18 were accepted into the study. One hundred and fifty four (87%) subjects completed the study. One EPA subject discontinued due to worsening depression, and one placebo subject discontinued due to an unspecified "negative reaction" to pills.

Interventions: Subjects were randomized to 8 weeks of double-blind treatment with oral EPA 1000 mg/day, DHA 1000 mg/day, or placebo.

Main Outcome Measures: Efficacy was assessed based on improvement in the HAM-D-17, Quick Inventory of Depressive Symptomatology (QIDS-SR), and the Clinical Global Improvement-Severity Scale (CGI-S).

Results: Modified Intent-to-Treat (MITT) analysis comprised 177 subjects with ≥1 post-baseoline visit (59.3% female, mean age 45.8 ± 12.5 years), and employed mixed model repeated measures (MMRM). The 3 groups demonstrated improvement in the HAM-D-17, QIDS-SR, and CGI-S ratings, but neither active treatment reached a threshold of statistical significance compared to placebo ($P > 0.05$). Effect size analysis demonstrated a modest advantage for EPA over placebo and over DHA, while placebo had a minimal advantage over DHA, with regard to HAM-D-17 and CGI-S scores. Response rates (based on ≥ 50% improvement in HAM-D-17 scores) were in the range of 40-50% for each treatment, and remission rates (final HAM-D-17 score ≤ 7) were in the range of 30%, with no significant differences between any groups.

Conclusions and Relevance: Neither EPA nor DHA monotherapy was superior to placebo for the treatment of MDD. These results suggest that omega-3s are not an effective monotherapy for MDD.

Trial Registration: ClinicalTrials.gov Identifier: NCT00517036

Key Words: Eicosapentaenoic Acid; EPA; docosahexaenoic Acid; DHA; omega-3; fatty acids; major depressive disorder

Introduction

Omega-3 fatty acid supplementation is a popular treatment for a wide range of indications, including cardiovascular disease and mood disorders. While it has been long accepted that consumption of omega-3 fatty acids supports cardiovascular health, recent systematic reviews have been less supportive of omega-3s as preventive agents for cardiovascular disease[1,2], although there remains support for their beneficial effects in individuals with metabolic syndrome[3].

Recent meta-analyses have also cast doubt on the putative antidepressant efficacy of the omega-3s[4-7]. There are currently more than 30 published clinical trials suggesting varying degrees of efficacy for omega-3 fatty acid treatment of major depressive disorder (MDD)[4-8], and for the depressive phase of bipolar disorder[9]. Most of these studies investigated combination preparations of eicosapentaenoic acid (EPA) plus docosahexaenoic acid (DHA) or EPA alone, with very few studies examining DHA alone. The majority of these publications examine omega-3 treatment as augmentation therapy in partial responders to standard antidepressants[4-8]. There are only two published studies of DHA monotherapy for MDD, one of which found no benefit of 2 g/day DHA versus placebo[10], whereas an uncontrolled dose-finding study by our group[11] found an advantage for DHA 1 g/day compared to 2 g/day and 4 g/day.

A meta-analysis by Sublette and colleagues[6] suggested that preparations containing > 60% EPA relative to DHA were more effective than those with a higher fraction of DHA. On the other hand, Lewis and colleagues[12] found a beneficial effect of serum DHA over EPA for preventing suicide in a military

sample. While the literature as a whole supports modest efficacy for omega-3 fatty acids, especially as adjuvant treatments for MDD, the question of whether EPA is a superior antidepressant to DHA, particularly as monotherapy, remains unanswered. We carried out a randomized placebo-controlled, double-blind clinical trial of EPA versus DHA for nonmedicated adults with MDD. At the time of the study design, our group had preliminary positive data for both EPA and DHA in depressed patient samples[11,13,14]. Thus, we postulated that EPA and DHA monotherapy would be more effective than placebo in the treatment of subjects with major depressive disorder[KB2].

Methods

The study population was derived from outpatients with MDD at Massachusetts General Hospital (MGH) and at Cedars-Sinai Medical Center (CSMC). The study was approved by the institutional review boards of both sites. Prior to initiating participation, all subjects signed a written informed consent form that they reviewed and discussed with a study physician.

Three hundred and eighty-nine outpatient subjects with MDD, ages 18-80, were recruited from 05/18/06 to 06/30/11 through advertisements and referrals from various outpatient programs. Inclusion criteria were a diagnosis of MDD according to the Structured Clinical Interview for DSM-IV – Axis I Disorders – Patient Edition (SCID I/P)[15], a Clinical Global Impressions-Severity[16] (Guy, 1976)[KB3] score ≥ 3, and a baseline HAM-D-17[17-19] score ≥ 18.

Participants filled out the Food Processor 7.8 questionnaire (ESHA Research Inc, Salem, OR)[20] for three consecutive days between screening and baseline visit to assess their dietary intake of omega-3 polyunsaturated fatty acids (PUFAs). Data from this questionnaire were analyzed at the baseline visit prior to randomization. Subjects with an average daily intake of ≥ 3.0 gm [KB4]of total omega-3 PUFA (as determined by a three-day dietary intake analysis) were excluded from the study. The average value of 3.0 gm[KB5]/day (for the past three days) was decided upon so as not to exclude a patient for the occasional intake of larger quantities of omega-3 PUFA. Subjects were asked not to significantly modify their diet during the 8 weeks of the study.

Subjects were excluded from participation in the study for the following reasons: pregnant women or women of child bearing potential who were not

using a medically accepted means of contraception (defined as oral contraceptive pill or implant, condom, diaphragm, spermicide, intrat-uterine device, s/p tubal ligation, partner with vasectomy); subjects who, in the investigator's judgment, were suicidal or homicidal; potential subjects with serious or unstable medical illness including cancer, cardiovascular, hepatic, renal, respiratory, endocrine, neurologic, autoimmune, or hematologic disorders; the following DSM-IV diagnoses (any current or past history, except substance abuse disorders) were exclusionary: organic mental disorders, substance use disorders, including alcohol, active within the last six months, schizophrenia, schizoaffective disorder, delusional disorder, psychotic MDD, psychotic disorders not elsewhere classified, and bipolar disorder; also excluded were subjects with a history of multiple adverse drug reactions or allergy to the study drugs, subjects with current use of psychotropic medications, systematic corticosteroid or steroid antagonists or other immunosuppressant agents, subjects who had failed to respond during the course of their current major depressive episode to at least one adequate antidepressant trial, defined as six weeks or more of treatment with citalopram 40 mg/day (or its antidepressant equivalent), or who had taken at least 1 g/day of **omega** omega-3 fatty acids, subjects who had had electroconvulsive therapy (ECT) within 6 months of the baseline evaluation, subjects who were taking supplements enriched with omega-3 fatty acids (e.g. flax seed oil), subjects taking anticoagulants or having a history of a bleeding disorder, and subjects who were in psychotherapy. Other exclusion criteria included: smoking > 10 cigarettes per day; vitamin E supplementation > 400 IU; menstruating individuals not able to have baseline and post-treatment bloods

drawn during the follicular phase; individuals not able to refrain from non-steroidal anti-inflammatory use for > 72 hours prior to blood work.

Eligible subjects returned for their baseline visit one week after the screen visit, a period during which no psychotropic medication was to be taken. Subjects with a Clinical Global Impression-Improvement (CGI-I) Scale[16] score of 1 or 2 (i.e., "much improved" or "very much improved") during the baseline visit were excluded from the study.

Subjects who entered the study were randomized in a 1:1:1 manner to 1g/day of EPA-enriched mix, 1g/day DHA-enriched mix[KB6], and placebo for 8 weeks. The omega-3 preparations and placebo were donated by NordicNaturals. Randomization and treatment assignment were carried out by the research pharmacies of the two institutions using their standard allocation procedures and a fixed block size of 30 subjects (MGH) or a randomly permuted block size between 6 and 15 subjects (CSMC). Only blind treatment codes, coordinated between the two site pharmacies, were noted on randomization lists provided to study staff. All members of the research team (including clinicians, research assistants, and study participants) remained blind to actual treatment assignment throughout the study. Analyses of primary and secondary measures of depression severity were carried out based on blind treatment codes. **, using an online randomization calculator, and dDouble blind medications were provided to each research team such that neither the clinicians, research assistants or study participants knew what each patient was receiving.**

Patients were instructed to take **initially** 2 EPA capsules plus 2 identical placebo capsules, or 4 DHA capsules, or 4 placebo capsules, every**in the**

morning. According to the randomization of that particular patient, the pill bottles contained EPA-enriched mix (ProEPAxtra, 1060 mg EPA / 274 mg DHA per 2 soft gels), or DHA-enriched mix (ProDHA, 450 mg DHA / 90 mg EPA per 2 soft gels), or placebo (1000 mg soybean oil, or about 50% linoleic acid (n-6) and 8% linolenic acid (n-3)). A double-dummy placebo design was used to maintain double-blind status, since the DHA capsules differed in appearance from the EPA capsules. Each patient took capsules from two bottles, with one bottle containing either DHA or DHA-placebo and the other bottle containing either EPA or EPA-placebo, depending on the randomization. Medication compliance was determined by pill count based on bottles returned at the next visit.

Subjects were evaluated every 2 weeks for 8 weeks during the course of the study. Clinical outcome measures assessed at every study visit included the HAM-D-17 score (the primary outcome measure), CGI-S and CGI-I scores, Quick Inventory of Depressive Symptomatology, Self-Rated[21] scores, the Well-Being Scale[22] scores, and the Quality of Life Satisfaction Questionnaire (Q-LES-Q)[23] scores.

*Statistical**s and Outcomes** Analyses*

Descriptive statistics were obtained for the 3 treatment groups, based on a modified intent-to-treat sample consisting of 177 evaluable subjects (those with at least one post-baseline visit). Comparisons across treatment groups at baseline were made by means of ANOVA for continuous measures and chi-squared tests for categorical variables.

Mixed model repeated measure analysis (MMRM[KB7]) was carried out to examine changes from baseline to treatment week 8 on measures of depressive severity, well-being, and quality of life. **for all evaluable subjects, defined as those having data for at least one post-baseline visit.**

Treatment response was defined as having an improvement of ≥ 50% in HAM-D-17 score from baseline to study completion, and remission was defined as having a final HAM-D-17 score ≤ 7 at study completion. Comparisons in response and remission rates between treatment groups, and in CGI improvement scores, were made using chi-squared analysis.

Adverse effects were measured using the PRISE instrument[24]. Because many subjects endorsed PRISE symptoms at baseline, the analysis focused on adverse events that emerged or worsened during the course of treatment. Comparisons between treatment groups were made using ANOVAs and chi-squared tests.

Results

Of the 389 screened patients, 196 (53% female, mean age 44.7 ± 13.4 years) were randomized. Nineteen subjects dropped out before completing at least one post-baseline visit, leaving 177 evaluable subjects. Patient flow is illustrated in Figure 1.

Table 1 summarizes demographic characteristics and baseline clinical variables for the evaluable study sample. Per guidelines of the National Institutes of Health (NIH), race and ethnicity, as self-defined by the participants, were recorded to reflect the population distributions of each site. No significant differences were found among the three treatment groups, with the exception of employment status, which was noted for a significantly higher employment rate in the DHA group compared to the other two groups (p=0.041). Over a quarter of subjects had a current non-primary anxiety disorder (26.5%) or a lifetime anxiety disorder (31.2%), and 14.7% had their current MDD superimposed on underlying dysthymia (eTable 1).

One hundred and fifty four (87%) of the evaluable subjects completed the study. We examined baseline characteristics of completers versus noncompleters to determine whether there were any significant differences between the two groups. Completers [KB8]were more likely to be employed and to be participants at the Cedars-Sinai clinical site. Otherwise no significant differences were noted in age, gender, race or ethnicity, marital status, education level or baseline values of any of the main outcome measures including the HAM-D-17, QIDS-SR, CGI-S, Q-LESQ, and WBS (eTable 2).

Table 2 summarizes change from baseline to treatment week 8 for the 177 evaluable subjects (59.3% female, mean age 45.8 ± 12.5 years), based on **mixed model repeated measures (**MMRM**)** analysis. All 3 groups experienced improvement in the HAM-D-17, QIDS-SR, CGI-S, Q-LES-Q, and the six WBS scales, but none attained statistical significance based on treatment-by-time interaction. Effect size analysis suggested a modest advantage for EPA over placebo and over DHA, while placebo had a minimal advantage over DHA, with regard to HAM-D-17 and CGI-S scores.

Table 3 compares response and remission rates for evaluable subjects in the three treatment arms. Response rates (based on ≥ 50% improvement in HAM-D-17) fell in the range of 40-50% for each treatment, and remission rates (based on final HAM-D-17 ≤ 7) were in the range of about 30%, with no significant differences between treatment groups. Group differences based on CGI severity and improvement thresholds were also non-significant.

Table 4 summarizes the tolerability data for the safety sample that included 173 subjects with available data. The 3 groups had similar levels of symptoms endorsed at baseline: between 20 and 30% of subjects endorsed some baseline physical or depressive symptoms on the PRISE (Table 4). eTable 3 summarizes all recorded PRISE symptoms at baseline. No significant differences across treatment groups were observed for the number of AEs emerging or worsening, or for those emerging or worsening to a distressing level during this study (Table 4). However, we found that a significantly greater number of subjects in the DHA-treatment group reported emerging or worsening physical symptoms compared to subjects in the other two groups (P=0.042). Of

the 21 specific physical symptoms assessed with the PRISE (eTable 4), only constipation was significantly different by treatment group (13.3% for EPA, 14.3% for DHA, and 0.0% for placebo; P=0.010). Few patients discontinued from the study because of treatment-related adverse effects; one EPA subject discontinued due to "negative reaction to pills" (worsening depression), and one placebo patient discontinued due to an unspecified "negative reaction to pills" (Figure 1).

Discussion

The omega-3 fatty acids EPA and DHA were well tolerated, but did not demonstrate an advantage over placebo-treatment of subjects with major depressive disorder in this trial. All three treatment arms experienced a 9-10 point improvement in their HAM-D-17 severity scores, with EPA conferring the greatest benefit and DHA the least. The three groups also**did not** failed to differ significantly on measures of well-being, quality of life, or secondary symptoms of depression. Response and remission rates were lower than expected for the active treatments, based on what is known about the efficacy of established antidepressants[25]. EPA had the highest remission rate of the 3 groups, and a small effect size advantage, although again there were no significant differences among the groups. Subjects randomized to DHA did report the emergence of slightly more physical side effect symptoms, but **otherwise** the three groups did not differ significantly in terms of the tolerability of study compounds.

Our findings suggest that neither EPA nor DHA alone is sufficient treatment for subjects with major depressive disorder[KB9]. The small effect size difference favoring EPA over both DHA and placebo is intriguing; although speculative, it may suggest that EPA *supplementation* might be a useful augmenting agent. Mozaffari-Khosravi and colleagues[26] reported that adjunctive 1 g/day EPA caused significantly greater reductions in HAM-D-17 scores than 1 g/day DHA in antidepressant-treated subjects with major depressive disorder [KB10]followed for 12 weeks. These findings agree with a recent paper by Gertsik and colleagues[14] who found that EPA augmentation was significantly more efficacious than placebo augmentation of citalopram-treated subjects with major

depressive disorder. Both of these reports are consistent with a new meta-analysis suggesting that EPA may be more beneficial as an augmenting agent rather than as monotherapy[27].

As is the case with all clinical trials, our study is subject to a number of limitations. Obtaining an adequate sample size is always a concern in two-site trials like this one: potential participants with MDD may be reluctant to enter a placebo-controlled study, may choose to purchase omega-3 fatty acids over the counter, or may prefer more established pharmacotherapies or psychotherapies. However, our sample is large enough to provide a conclusive statement about the efficacy of EPA and DHA as monotherapies for major depressive disorder[KB11], and we did not discern a clinically meaningful difference.

The placebo response rate (47.5%) could have impeded signal detection, since a meta-analysis of randomized controlled trials of antidepressants found that if a study exceeds a 40% response rate to placebo, it is **less** unlikely to show a statistically significant effect of the active agent[28]. T**Although t**he original target sample size of 100 subjects per treatment arm was expected to have 80% power to detect an effect size $\geq$ 0.40 between pairs of treatment groups, however, we performed a masked interim analysis that indicated there was no difference between the three treatment groups and continuing recruitment would unnecessarily expose subjects to ineffective interventions. **the magnitude of improvement found for the placebo group makes it highly unlikely that a larger sample size would have resulted in a statistically significant or clinically meaningful difference for either active treatment vs. placebo.** In this study we did not measure our subjects' expectancy and credibility of

treatment effect, but it would not be unreasonable to wonder if our placebo response rate was influenced by a combination of subject expectancy as well as the very benign side effect profile of the treatments employed in this study. We also controlled for site-related differences in this trial. Of the 177 evaluable subjects, 108 were from CSMC**Cedars-Sinai Health Center (CSHC)** and 69 from MGH (eTable 2). While the CSM**HC** subjects in each treatment arm fared somewhat better than their MGH counterparts, there were no significant site-related differences in clinical improvement (not shown).

How should these findings be interpreted in the context of the existing literature? Our results suggest that omega-3 fatty acid supplementation is not an effective *monotherapy* for patients with major depressive disorder[KB12]. This seems consistent with data regarding omega-3 supplementation for other conditions[1,2]. Our results differ from epidemiologic studies that examine populations where individuals consume more foods rich in omega-3 fatty acids and fewer foods rich in omega-6 fatty acids[29], because in our study individuals were allowed to consume their usual omega-6 rich diet. Thus, we attempted to use a supplement to modify the omega-3/omega-6 ratio rather than a dietary intervention that both increases omega-3 intake while decreasing omega-6 intake.

In summary, this study, the first head-to-head comparison of EPA versus DHA monotherapy for major depressive disorder[KB13], failed to show a significant difference between EPA, DHA, and placebo. Further investigation of the omega-3s in mood disorders should focus on augmentation therapy of depressed patients. Related analyses of our patient sample are in progress to examine

factors such as levels of plasma lipids and inflammatory markers as potential moderators or mediators of treatment response. These results may yield greater insight as to whether certain subsets of depressed individuals may be better candidates for omega-3 treatment.

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Only the authors were responsible for the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, and approval of the manuscript. The sponsors played no role in any of the above.

Drs. Mischoulon, Rapaport, and Schettler had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Disclosures

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Dr Rapaport has provided consulting services to Affectis Pharmaceutics, Methylation Sciences, PAX Pharmaceuticals, and Johnson & Johnson Pharmaceuticals. He has served on the Scientific Advisory Boards of NIMH, Bipolar Disorder and Depression Alternative Treatment foundation. He served on a DSMB for NIDA and Quintiles (for an Astra Zeneca protocol).

The remaining authors report no conflicts of interest.

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Table 1
Demographic and Clinical Characteristics[KB14], Overall and by Treatment Group
of N=177 Evaluable Subjects in 8-Week Study of EPA vs. DHA vs. Placebo for Treatment of Major Depression

Characteristic			All Evaluable Subjects (N=177)	EPA (N = 60)	DHA (N = 58)	Placebo (N = 59)	Significance		
							x^2	df	P
Demographics									
Study Site Hosp.	Cedars-Sinai Medical Center	N (%)	108 (61.0)	38 (63.3)	33 (56.9)	37 (62.7)	0.62	2	0.733
	Massachusetts General	N (%)	69 (39.0)	22 (36.7)	25 (43.1)	22 (37.3)			
Gender	Male	N (%)	72 (40.7)	22 (36.7)	26 (44.8)	24 (40.7)	0.81	2	0.666
	Female	N (%)	105 (59.3)	38 (63.3)	32 (55.2)	35 (59.3)			
Race	Caucasian	N (%)	120 (67.8)	42 (70.0)	38 (65.5)	40 (67.8)	5.77 [b]	6	0.449
	African American	N (%)	32 (18.1)	13 (21.7)	8 (13.8)	11 (18.6)			
	Other	N (%)	15 (8.5)	3 (5.0)	6 (10.3)	6 (10.2)			
	Prefer Not to Say	N (%)	10 (5.6)	2 (3.3)	6 (10.3)	2 (3.4)			
Ethnicity [a]	Hispanic	N (%)	27 (15.8)	10 (17.2)	9 (15.8)	8 (14.3)	0.19	2	0.911
	Non-Hispanic	N (%)	144 (84.2)	48 (82.8)	48 (84.2)	48 (85.7)			
Education [a]	H.S. or Less	N (%)	44 (26.0)	17 (28.8)	15 (26.3)	12 (22.6)	0.56	2	0.757
	Some College or More	N (%)	125 (74.0)	42 (71.2)	42 (73.7)	41 (77.4)			
Marital Status [a]	Married/Live Together	N (%)	31 (19.5)	11 (20.4)	10 (19.2)	10 (18.9)	1.19	4	0.879
	Sep./Wid./Divorced	N (%)	53 (33.3)	19 (35.2)	19 (36.5)	15 (28.3)			
	Never Married	N (%)	75 (47.2)	24 (44.4)	23 (44.2)	28 (52.8)			
Employment Status [a]	Employed	N (%)	81 (47.6)	26 (44.1)	34 (58.6)	21 (39.6)	13.15 [b]	6	**0.041**
	Homemaker	N (%)	8 (4.7)	3 (5.1)	3 (5.2)	2 (3.8)			
	Student	N (%)	11 (6.5)	3 (5.1)	0 (0.0)	8 (15.1)			
	Other	N (%)	70 (41.2)	27 (45.8)	21 (36.2)	22 (41.5)			

Age	Mean (sd) [N] (Range)	45.8 (12.5) [167] (21-73)	46.2 (11.8) [57] (21-73)	46.3 (13.7) [55] (23-70)	45.0 (12.1) [55] (22-69)	F 0.19	df 2, 164	P 0.831
Clinical Measures						F	df	P
Hamilton Depression Rating Scale - 17-Item Version ($HAM\text{-}D_{17}$)	Mean (sd) [N]	19.5 (3.4) [177]	19.3 (3.8) [60]	19.8 (3.2) [58]	19.2 (3.1) [59]	0.62	2, 174	0.542
Quick Inventory of Depressive Symptomatology - Self-Report ($QIDS\text{-}SR_{16}$)	Mean (sd) [N]	13.2 (4.1) [173]	12.9 (3.9) [60]	13.3 (4.5) [58]	13.5 (3.8) [55]	0.30	2, 170	0.738
Clinical Global Impression – Severity of Depression (CGI-S)	Mean (sd) [N]	4.1 (0.6) [174]	4.2 (0.6) [59]	4.2 (0.7) [57]	4.0 (0.6) [58]	1.64	2, 171	0.198
Quality of Life Enjoyment & Satisfaction(Q-LES-Q)								
% of Max. Possible, Items 1-14	Mean (sd) [N]	43.5 (13.6) [171]	43.5 (15.4) [58]	41.6 (12.7) [56]	45.3 (12.7) [57]	1.07	2, 168	0.347
% Standardized Around Norms	Mean (sd) [N]	-3.1 (1.2) [171]	-3.1 (1.3) [58]	-3.2 (1.1) [56]	-2.9 (1.1) [57]	1.07	2, 168	0.347
Psychological Well-Being Scale (WBS) Scores (Standardized by Gender):								
Environmental Mastery	Mean (sd) [N]	-3.0 (1.2) [174]	-3.0 (1.2) [60]	-2.9 (1.3 [57]	-3.2 (1.1) [57]	0.68	2, 171	0.508
Self-Acceptance	Mean (sd) [N]	-2.7 (1.2) [173]	-2.9 (1.1) [59]	-2.6 (1.1) [57]	-2.7 (1.3) [57]	0.86	2, 170	0.425
Purpose in Life	Mean (sd) [N]	-1.9 (1.1) [174]	-1.9 (1.1) [60]	-2.0 (1.1) [57]	-1.9 (1.2) [57]	0.27	2, 171	0.766
Positive Relations with Others	Mean (sd) [N]	-1.6 (1.3) [172]	-1.6 (1.3) [59]	-1.7 (1.2) [57]	-1.5 (1.3) [56]	0.53	2, 169	0.588
Personal Growth	Mean (sd) [N]	-1.1 (1.2) [171]	-1.1 (1.2) [60]	-1.0 (1.1) [55]	-1.1 (1.3) [56]	0.19	2, 168	0.828
Autonomy	Mean (sd) [N]	-0.7 (1.2) [174]	-0.7 (1.3) [60]	-0.8 (1.3) [57]	-0.7 (1.1) [57]	0.13	2, 171	0.877

a. Information is missing for some subjects.
b. x^2 may not be valid because of the number of cells with expected count < 5.

Table 2
Change from Baseline to Treatment Week 8 for N=177 Evaluable Subjects Based on Mixed Model Repeated Measures Analysis[a]

Assessment Scale	Least-Square Means (se) of Change at Treatment Week 8			Significance of Treatment-by-Time Interaction			Standardized Effect Size at Week 8[d]		
	EPA LS-Mean (se) [N]	DHA LS-Mean (se) [N]	Placebo LS-Mean (se) [N]	F	df[c]	P	EPA vs. Placebo	DHA vs. Placebo	EPA vs. DHA
Depression:									
Hamilton Depression Rating Scale - 17-Item Version ($HAM\text{-}D_{17}$)	- 10.34 (0.62) [60]	- 9.26 (0.62) [58]	- 9.49 (0.61) [59]	0.23	2, 687	0.794	- 0.179	+ 0.049	- 0.228
Quick Inventory of Depressive Sympto-matology - Self-Report ($QIDS\text{-}SR_{16}$)	- 5.01 (0.47) [60]	- 4.79 (0.47) [58]	- 5.54 (0.47) [56]	0.39	2, 715	0.676	+ 0.148	+ 0.211	- 0.061
Clinical Global Impression – Severity of Depression (CGI-S)	- 1.46 (0.11) [59]	- 1.33 (0.11) [57]	- 1.41 (0.11) [58]	0.07	2, 682	0.937	- 0.061	+ 0.090	- 0.151
Quality of Life Enjoyment & Satisfaction: Q-LES-Q % of Max. Possible, Items 1-14	+ 11.05 (1.40) [59]	+ 10.89 (1.39) [57]	+ 11.13 (1.38) [59]	0.01	2, 733	0.990	- 0.007	- 0.023	+ 0.01$
Psychological Well-Being Scale:									
WBS Scores (Standardized by Gender):									
Environmental Mastery	+ 0.68 (0.11) [60]	+ 0.58 (0.11) [57]	+ 0.78 (0.11) [57]	0.17	2, 724	0.842	- 0.119	- 0.241	+ 0.119
Self-Acceptance	+ 0.53 (0.11) [59]	+ 0.69 (0.11) [57]	+ 0.49 (0.11) [57]	0.81	2, 730	0.444	+ 0.048	+ 0.241	- 0.191
Purpose in Life	+ 0.32 (0.11) [60]	+ 0.54 (0.11) [57]	+ 0.65 (0.11) [57]	0.86	2, 717	0.425	- 0.392	- 0.132	- 0.261
Positive Relations with Others	+ 0.31 (0.10) [59]	+ 0.59 (0.10) [57]	+ 0.49 (0.10) [56]	0.58	2, 718	0.562	- 0.237	+ 0.133	- 0.368
Personal Growth	+ 0.59 (0.10) [60]	+ 0.33 (0.10) [55]	+ 0.37 (0.10) [56]	1.22	2, 711	0.295	+ 0.289	- 0.054	+ 0.343
Autonomy	+ 0.32 (0.09) [60]	+ 0.21 (0.09) [57]	+ 0.49 (0.09) [57]	0.70	2, 702	0.498	- 0.247	- 0.412	+ 0.160

a. The above assessments were administered at Baseline and at 2-week intervals during the 8-week study. MMRM analyses were performed on change from Baseline to Week 8 for these measures. A full-model MMRM was performed testing the significance of effects of treatment, visit, and treatment-by-visit interaction, as well as the covariates of site, baseline score and baseline score-by-visit interaction.

b. Change at 8 weeks is significantly different from zero for each treatment group on every assessment in the table, at $P \leq 0.001$ with two exceptions: (1) EPA group on WBS Purpose in Life ($P=0.004$) and DHA group on WBS Autonomy ($P=0.018$).

c. Degrees of freedom are determined using the Satterthwaite approximation method.

d. By Cohen's *d* effect size = (difference between LS-Mean change) / pooled sd for each pair of treatments (sd per group computed from se of LS-Mean from MMRM).
For depression scales, a negative effect size indicates that the 1st group improved more than the 2nd one (has a lower negative LS-mean change).
For Q-LES-Q and WBS scores, a positive effect size indicates **indicates** that the 1st group improved more than the 2nd one (has a higher positive LS-mean change)

Table 3
Binary Measures of Outcome by Last Treatment Visit for N=177 Evaluable Subjects

Binary Measure of Outcome	Treatment Group EPA N (%) [Total N]	DHA N (%) [Total N]	Placebo N (%) [Total N]	Significance
Hamilton Depression Rating Scale 17-ItemVersion (HAM-D17)				
Remitter (Total Score ≤7)	20 (33.3) [60]	16 (27.6) [58]	19 (32.2) [59]	x^2=0.508; df=2; P=0.776
Responder (Decrease ≥50% from Baseline)	26 (43.3) [60]	26 (44.8) [58]	28 (47.5) [59]	x^2=0.209; df=2; P=0.901
CGI - Severity Rating				
Normal or Only Borderline Mentally Ill (Value 1 or 2 on 7-Point Scale)	22 (37.3) [59]	18 (31.6) [57]	25 (43.1) [58]	x^2=1.632; df=2; P=0.442
CGI - Improvement Rating				
Very Much or Much Improved (Value 1 or 2 on 7-Point Scale)	34 (57.6) [59]	28 (49.1) [57]	31 (53.4) [58]	x^2=0.843; df=2; P=0.656

Table 4
Summary of PRISE Items[a] Endorsed at Baseline and Adverse Events (AEs) Emerging or Worsening during 8-Week Study of EPA vs. DHA vs. Placebo for Treatment of Major Depression for N=173 Subjects in Safety Sample, by Treatment Group

PRISE Item or Subject Count		EPA (N=60)	DHA (N=56)	Placebo (N=60)	χ^2 and Significance (df=2)[b]
ITEMS ENDORSED AT BASELINE					
Number of Items Endorsed					
Physical Symptoms	Mean (sd) [Range]	1.0 (2.4) [0-13]	1.0 (2.0) [0-10]	0.9 (1.9) [0-9]	Kruskal-Wallis χ^2 =0.236; P=0.889
Depressive Symptoms	Mean (sd) [Range]	1.2 (2.6) [0-9]	1.6 (2.9) [0-10]	1.8 (2.9) [0-9]	Kruskal-Wallis χ^2 =1.061; P=0.588
Subjects with Any Item(s) Endorsed					
Physical Symptoms	N (%)	15 (25.0)	16 (28.6)	16 (26.7)	χ^2 =0.189; P=0.910
Depressive Symptoms	N (%)	14 (23.3)	15 (26.8)	19 (31.7)	χ^2 =1.060; P=0.589
Number of Items at Distressing Level					
Physical Symptoms	Mean (sd) [Range]	0.3 (1.2) [0-9]	0.1 (0.3) [0-2]	0.2 (0.6) [0-4]	Kruskal-Wallis χ^2 =1.908; P=0.385
Depressive Symptoms	Mean (sd) [Range]	0.4 (1.5) [0-9]	0.2 (1.0) [0-6]	0.6 (1.6) [0-6]	Kruskal-Wallis χ^2 =3.059; P=0.217
Subjects with Any Distressing Item(s)					
Physical Symptoms	N (%)	6 (10.0)	2 (3.6)	5 (8.3)	χ^2 (Yates) =1.869; P=0.393 [e]
Depressive Symptoms	N (%)	6 (10.0)	5 (8.9)	11 (18.3)	χ^2 =2.863; P=0.239
AEs EMERGING OR WORSENING DURING TREATMENT					
Number of AEs Emerging or Worsening [c]					
Physical Symptoms	Mean (sd) [Range]	2.7 (4.6) [0-25]	2.8 (3.5) [0-14]	2.4 (4.7) [0-21]	Kruskal-Wallis χ^2 =4.962; P=0.084
Depressive Symptoms	Mean (sd) [Range]	2.2 (3.6) [0-18]	2.5 (4.2) [0-21]	3.4 (6.8) [0-30]	Kruskal-Wallis χ^2 =0.128; P=0.938
Subjects with Any AE Emerging/Worsening					
Physical Symptoms	N (%)	33 (55.0)	39 (69.6)	28 (46.7)	χ^2 =6.355; P=0.042
Depressive Symptoms	N (%)	28 (46.7)	24 (42.9)	23 (38.3)	χ^2 =0.854; P=0.652
Number of AEs Emerging/Worsening to a Distressing Level [d]					
Physical Symptoms	Mean (sd) [Range]	0.2 (0.7) [0-3]	0.5 (1.9) [0-13]	0.6 (1.6) [0-9]	Kruskal-Wallis χ^2 =0.507; P=0.776
Depressive Symptoms	Mean (sd) [Range]	0.5 (1.3) [0-5]	0.4 (0.9) [0-4]	1.0 (3.1) [0-17]	Kruskal-Wallis χ^2 =0.067; P=0.967
Subjects with Any AE Emerging/Worsening to a Distressing Level					

Physical Symptoms	N (%)	10 (16.7)	9 (16.1)	12 (20.0)	χ^2 =0.364; P=0.834
Depressive Symptoms	N (%)	11 (18.3)	10 (17.9)	11 (18.3)	χ^2 =0.006; P=0.997

Footnotes for Table 5:

a. PRISE physical symptoms (items 1-21) include gastrointestinal, heart, skin, nervous symptoms, eyes/ears, and genital/ urinary, plus "other" (item 33) which were all physical symptoms in this sample. Depressive symptoms (items 22-32) include sleep difficulty, sexual dysfunction, anxiety, poor concentration, general malaise, restlessness, fatigue, and decreased energy.

b. The distribution of values for number of items/symptoms is highly non-normal, so comparison of treatment groups was by Kruskal-Wallis χ^2 on Wilcoxon Rank Sums (after assigning tied values their mean rank). For number of subjects with a baseline or emerging/worsening category of symptoms, χ^2 was calculated with Yates' correction if any expected frequency was less than 5.

c. +1 was added to the count for *each* post-baseline visit in which an adverse event rating exceeded its value at baseline (on a scale where 0 = absent; 1 = tolerable; 3 = distressing).

d. +1 was added to the count for *each* post-baseline visit in which an adverse event reached the distressing level, but was either absent or tolerable at baseline.

e. χ^2 test may not be valid due to 50% of cells having expected frequency less than 5.

Full Title: Efficacy of Massage and Touch Therapy for the Treatment of Cancer-Related Fatigue (CRF) in Breast Cancer Survivors

Short Title: mCRF

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PRÉCIS

Study Title

Efficacy of Massage and Touch Therapy for the Treatment of Cancer-Related Fatigue (CRF) in Breast Cancer Survivors

Objectives

Primary Aim: To conduct a feasibility study to determine whether a 6-week SMT intervention can decrease CRF, as measured by the Multidimensional Fatigue Inventory (**MFI**), among breast cancer survivors who have received both radiation and chemotherapy and have CRF. We hypothesize that SMT will decrease fatigue more than LT or WLC as assessed by the MFI.

Secondary Aim: To determine whether the hypothesized decrease in CRF is due to SMT modulating the immune system of subjects with CRF to decrease chronic inflammation.

Exploratory Aims:

1. To explore the relationship between measures of fatigue and QOL as assessed by the MFI and the Patient–Reported Outcomes Measurement System (**PROMIS**).
2. To explore the relationship between the decrease in CRF caused by SMT or LT and pre-treatment credibility, expectancy, and preference scores.

Design and Outcomes

This study is a wait-list controlled clinical trial to test the efficacy of Swedish massage therapy on cancer related fatigue in women, ages 18 to 65, 6 months post treatment for Stage 0-IIIA breast cancer.[KB1]

Eligible subjects will be randomized to one of three treatment groups:

1) Massage therapy once per week for 6 weeks,
2) Light touch therapy once per week for 6 weeks, or
3) A 6 week wait, followed by randomization to massage therapy or light touch therapy once per week for 6 weeks.

Primary outcome is the Multidimensional Fatigue Inventory (**MFI**). Secondary outcomes are immune measures including whole blood mitogen stimulated assay, and cytokine/CRP determination.

Interventions and Duration

Eligible subjects will be randomized to one of three **treatment** groups:

1) Massage therapy once per week for 6 weeks,
2) Light touch therapy once per week for 6 weeks, or
3) A 6 week wait, followed by randomization to massage therapy or light touch therapy once per week for 6 weeks.

The total length of time on study for subjects randomized to treatment groups 1 and 2 is 6 weeks. The total length of time on study for subjects randomized to treatment group 3 is 12 weeks.

Sample Size and Population

Study participants will consist of women, ages 18 to 65, with Stage 0-IIIA breast cancer, status-post surgery treated with standard anthracycline- and/or taxane-based chemotherapy plus radiation (6 weeks of definitive whole breast or chestwall irradiation at a dose of 50.0 Gy with a 10-16 Gy boost). Patients will be between 6 months and 1-year post radiation treatment. Of note, the choice of this relatively homogenous group of patients minimizes the possibility of introducing variability due to differing treatment regimens and time since treatment completion. Subjects with a Brief Fatigue Inventory (BFI) score of >25 will be eligible to enter the study. This is a cut-off score used in other cancer-related fatigue (CRF) trials (Dimeo et al, 2008).

Approximately 72 survivors of breast cancer will be enrolled in this study (in order to have 60 complete, 20 per treatment group).

We will use variable sized, permuted block randomization.

Based on the findings from the study by Jean-Pierre et al. (A phase 3 randomized, placebo-controlled, double-blind, clinical trial of the effect of modafinil on cancer-related fatigue among 631 patients receiving chemotherapy. Cancer, 2010; doi: 10.1002/cncr.25083) we will stratify randomization within groups with severe vs. moderate baseline severity of fatigue, defined as a self-rating $\geq$7 on item 3 of the BFI at baseline (self-rating of worst level of fatigue during the past 24 hours, on a 0-10 scale).

Abstract:
With approximately 12 million cancer survivors today in the United States alone, increased attention is being given to quality of life after cancer treatment. Cancer-related fatigue (**CRF**) is one of the most prevalent and debilitating symptoms experienced by people with cancer. It can persist for months or years after cancer therapy is completed and has a negative impact on all areas of function. Meaningful evidence-based treatment options for CRF are extremely limited and finding safe, inexpensive, and effective interventions for managing this distressing symptom are urgently needed. Basic research on neural-immune interactions has shown that pro-inflammatory cytokines can cause potent changes in behavior including reduced activity, fatigue, and decreased social behavior. Furthermore, research over the last decade has correlated more debilitating levels of CRF with increased levels of pro-inflammatory cytokines. Thus, investigation of therapeutic modalities that may decrease pro-inflammatory cytokines, decrease hsCRP, and increase anti-inflammatory cytokines in the setting of CRF represents a plausible target for intervention. Massage therapy is one of the fastest growing alternative therapies and has a high rate of acceptance for symptom management among cancer patients. Massage has been shown in smaller studies with cancer patients to modulate the immune system. Moreover, massage has been demonstrated to significantly decrease pro-inflammatory cytokines in normal subjects. There are no published randomized controlled trials examining either the role of massage as an intervention primarily for CRF or investigating its anti-inflammatory effects as a mechanism for its hypothesized improvement in CRF. This proposal investigates the effects of massage therapy on CRF among a homogenous group of breast cancer survivors. Our primary hypothesis is that Swedish Massage Therapy (**SMT**) will decrease CRF compared to a light touch condition and wait list control. Our secondary hypothesis is that SMT will ameliorate CRF by decreasing levels of pro-inflammatory cytokines, decrease hsCRP, and increasing anti-inflammatory cytokines. Our main exploratory hypothesis is that a decrease in CRF will increase quality of life among cancer survivors.

1. Introduction and Background

With approximately 12 million cancer survivors today in the United States alone, increased attention is being given to quality of life after cancer treatment. Fatigue is the most common, and one of the most devastating symptoms among patients with cancer (Curt et al., 2000, Lawrence et al., 2004, Hofman et al., 2007). According to the National Comprehensive Cancer Network (**NCCN**) CRF is "a persistent, subjective sense of physical, emotional, and/or cognitive exhaustion related to cancer or its treatment that is not proportional to recent activity" (NCCN, 2011). Fatigue occurs across the spectrum of cancer types and treatments (Nail, 2004). CRF has a negative impact on all areas of function, including mood, physical function, work performance, social interaction, family care, cognitive performance, schoolwork, and community activities (Bower, 2005, Berger et al., 2009, NCI, 2010). CRF has been rated as more troublesome and to have a greater negative impact on quality of life than other cancer-related symptoms such as pain, depression, and nausea (Curt et al., 2000, Stone et al., 2000). CRF can persist for months or years after cancer therapy is completed (Bower et al., 2000, Curran et al., 2004, Hofman et al., 2007).

Meaningful evidence-based treatment options for CRF are extremely limited (Bruera and Yennurajalingam, 2010). A recent Cochrane Review found that the only viable pharmacologic treatment for CRF was methylphenidate, which causes a small but significant improvement in fatigue (Minton et al., 2010). There are few studies investigating non-pharmacologic treatment strategies for CRF although there are emerging data that exercise decreases CRF (Cramp and Daniel, 2008). A variety of different psychosocial interventions have been studied and have shown small but significant reductions in fatigue. Methodology and design challenges, however, limit the impact of this work (Stone and Minton, 2008).

One of the challenges with finding effective treatment options is identifying underlying mechanisms for CRF. There is growing interest in the role of the cytokine network in CRF. Basic research on neural-immune interactions have found that pro-inflammatory cytokines signal the central nervous system and exert potent effects on behavioral processes, including reduced activity, fatigue, decreased social and sexual behavior, and cognitive function (Schubert et al., 2007, Dantzer et al., 2008). These effects appear to be mediated by the impact of cytokines on the basal ganglia, which is involved in the regulation of motor activity and motivation. Indeed, several studies using a variety of immune stimuli, including pro-inflammatory cytokines, have shown that immune activation alters basal ganglia function which in turn correlates with symptoms of fatigue and motor slowing (Capuron et al., 2007, Brydon et al., 2008, Eisenberger et al., 2010, Capuron et al., In Press). Relevant to this application, one of the most extensively studied cancer survivor groups regarding inflammation and fatigue are breast cancer survivors. Several studies have reported increased inflammatory markers including soluble TNF-alpha receptor 2 (sTNFR2), interleukin (IL)-1 receptor antagonist (IL-1ra), soluble IL-6 receptor (sIL-6R) and c-reactive protein (CRP) in fatigued versus non-fatigued breast cancer survivors (Bower et al., 2000, Collado-Hidalgo et al., 2006, Bower et al., 2009). Increases in inflammatory markers in fatigued breast cancer survivors have also been identified at the level of gene expression, with increased expression of genes bearing response elements for the inflammatory mediator nuclear factor kappa B (NF-kB) in their promoter regions (Bower et al., 2011). Of note, blocking the inflammatory cytokine TNF-alpha has been shown to reduce fatigue in patients with advanced cancer (Monk et al., 2006). Thus, investigation of therapeutic modalities that may decrease inflammation and pro-inflammatory cytokines in the setting of CRF appear to be a fruitful line of study to pursue.

Over 50% of patients with cancer have used a complementary and alternative medicine (CAM) approach for symptom management and quality of life (Vapiwala et al., 2006). One of the widely employed CAM interventions is massage therapy. Most of the studies investigating massage for patients with cancer focus on depression, anxiety, or pain as the outcomes of interest (Hernandez-Reif et al., 2004, Hernandez-Reif et al., 2005, Jane et al., 2008, Kutner et al., 2008, Wilkinson et al., 2008, Listing et al., 2010, Krohn et al., 2011). One recent study has investigated the effect of massage on breast cancer-related symptoms and mood and a decrease in fatigue was noted (Listing et al., 2009). However, CRF was not the primary outcome measure and immune parameters were not measured. A number of the smaller studies have investigated the effect of massage or a light touch intervention on biological measures in cancer patients (Hernandez-Reif et al., 2004, Hernandez-Reif et al., 2005, Listing et al., 2010, Krohn et al., 2011). The most consistently reported findings have been an increase in NK cell numbers or activity and an increase in circulating lymphocyte numbers as a result of massage therapy (Hernandez-Reif et al., 2004, Hernandez-Reif et al., 2005, Billhult et al., 2009, Krohn et al., 2011). These findings are consistent with our overarching working hypothesis about the

mechanism of action of massage, which we have proposed studying in an RO-1: SMT modulates immune function and hormonal activity by influencing autonomic nervous system tone.

There are no published randomized controlled trials either examining the role of massage as an intervention for CRF or investigating the role that modulation of immune function may have on decreasing CRF. However, as stated by the Cochrane group, there is a need for well-controlled investigations employing manualized interventions, standardized ratings, and appropriate potential biomarkers (Jane et al., 2008).

In conclusion, while CRF is one of the most prevalent and debilitating symptoms that plagues cancer survivors, effective therapies for CRF do not exist. Recent data suggest that pro-inflammatory cytokines are involved in the genesis of CRF and represent a plausible target for intervention. As discussed below, SMT has significant anti-inflammatory effects in normal subjects. We know from previous work that there is a high rate of acceptance of CAM approaches for symptom management among cancer patients. Since massage is a known modulator of immune function, thoughtfully exploring SMT as an intervention for CRF is warranted.

This highly innovative R21 will link biological findings suggesting that CRF may be caused by an over-expression of pro-inflammatory and under expression of anti-inflammatory cytokines with a novel CAM treatment intervention. Our baseline cytokine data will serve as an opportunity to investigate the cytokine postulate in a homogeneous cohort of patients with CRF. A second significant innovation of this investigation is the use of an inexpensive, safe, manual therapy that will not by its nature cause drug-drug interactions as a treatment for CRF. Since manual therapies like massage and light touch are popular and widely employed by the lay public for a wide array of conditions, we believe that there will be a high degree of acceptance of these approaches for patients with CRF. A third innovative aspect of this study is the attempt to demonstrate the hypothesized benefit of SMT for CRF via modulation of immune function. A fourth innovative aspect is the use of measures of expectancy and credibility as a control for aspects of subject bias that might potentially confound study results. A fifth important innovation employed is the use of the NIH PROMIS outcomes. This will provide important preliminary data about the use of these measures both as a potential outcome for CRF and also as an outcome measure in a manual therapy study. A final innovative aspect of this study is the week 12 sampling point.: By including this data point, we not only obtain preliminary data about the potential sustained actions of SMT and LT but we can perform a within subjects analysis of the WLC cohort which will allow us to investigate intra-individual differences in response to SMT. Thus this exploratory grant incorporates a number of unique opportunities to advance knowledge about both the biology of CRF and SMT.

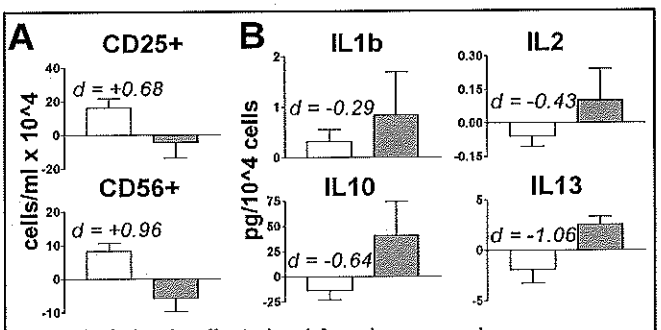
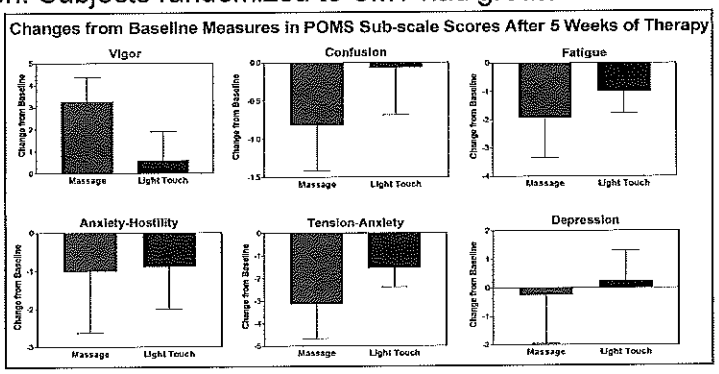


Fig. 1: Cohen's effect size (*d*) and measured cummulative change from baseline over 5wks of therapy (mean±SEM).

C. Preliminary Data Space limitations require that we present a fraction of our findings with the intent of demonstrating the feasibility and promise of our proposal. Our publication of the acute effects of massage in normal volunteers indicates a single session of SMT modulates immune parameters and stress-hormone levels (Rapaport et al., 2010). Twenty-nine subjects received one session of SMT and 24 received one session of LT. Blood samples for immune markers were collected 5 minutes before and 60 minutes after the 45-minute therapy session using similar methods to those in this application. Subjects randomized to SMT had greater increases in the numbers of circulating total lymphocytes, CD4+ and CD8+ cells, activated lymphocytes (CD25+) and NK cells (CD56+) than the LT group, and a blunting of pro-inflammatory Th-1 and Th-2 cytokine levels and an increase in anti-inflammatory cytokine concentrations as measured in an *in vitro* mitogen-stimulated whole blood assay. To investigate the long-term effects of SMT and the light touch control condition, we studied 15 SMT and 13 LT treated subjects who received 5 weekly sessions. We found a sustained effect of SMT on circulating activated



lymphocytes (CD25+) and NK cells (CD56+) (Fig.1A). The patterns observed for the effect of a single session on *in vitro* mitogen-stimulated levels of cytokines were sustained over the 5 weeks of study (Fig.1B). We also measured the impact of SMT (red) versus LT (blue) on psychological measures including fatigue and vigor (Figure2). Thus our preliminary data demonstrate that SMT modifies immune function, decreasing pro-inflammatory cytokines, increasing anti-inflammatory cytokines and decreasing fatigue and increasing vigor in normal volunteers.

2. Objectives

Primary Aim: To conduct a feasibility study to determine whether a 6-week SMT intervention can decrease CRF, as measured by the Multidimensional Fatigue Inventory (**MFI**), among breast cancer survivors who have received both radiation and chemotherapy and have CRF. We hypothesize that SMT will decrease fatigue more than LT or WLC as assessed by the MFI.

Secondary Aim: To determine whether the hypothesized decrease in CRF is due to SMT modulating the immune system of subjects with CRF to decrease chronic inflammation.

We hypothesize that:

a) SMT will cause a decrease in plasma concentrations of pro-inflammatory cytokines (IL-1β, IL-1Ra, IL-6, sIL-6R, TNF-α, sTNFR, IFN-γ), hsCRP and an increase in the anti-inflammatory cytokine (IL-10) more than LT or WLC.
b) SMT as compared to LT or WLC will cause a decrease in pro-inflammatory cytokines and an increase in anti-inflammatory cytokines as measured in an *in vitro* mitogen-stimulation assay.
c) A decrease in plasma pro-inflammatory cytokines, hsCRP and an increase in plasma anti-inflammatory cytokines will mediate the decrease in fatigue as assessed with the MFI.

Exploratory Aims:

1. To explore the relationship between measures of fatigue and QOL as assessed by the MFI and the Patient–Reported Outcomes Measurement System (**PROMIS**).
2. To explore the relationship between the decrease in CRF caused by SMT or LT and pre-treatment credibility, expectancy, and preference scores.
4. To analyze the within-subject effects of SMT versus WLC on immune function and fatigue scores for subjects initially randomized to the WLC, and to compare and contrast their change during SMT to that of the groups receiving SMT or LT during the first 6 weeks of the study.

2. Study Design

Subject Selection

This study is a wait-list .....controlled clinical trial to test the efficacy of Swedish massage therapy on cancer related fatigue in women, ages 18 to 65, 6 months post treatment for Stage 0-IIIA breast cancer.[KB2]

Approximately 72 survivors of breast cancer will be enrolled in this study (in order to have 60 complete), recruited through the Department of Radiation Oncology at Emory University. All potential subjects will be encouraged to discuss their participation with appropriate support systems prior to giving consent. Interested subjects will have either an initial phone interview or in-person interview with a study coordinator at a clinic visit to determine if the study might be a good fit. If an eligible subject decides to participate, a Screening Visit will be scheduled.

Eligibility Criteria

Inclusion criteria:

Participants must meet all of the inclusion criteria to participate in this study. Inclusion criteria include:

- Women
- ages 18 to 65
- with Stage 0-IIIA breast cancer, status-post surgery treated with standard anthracycline- and/or taxane-based chemotherapy plus radiation (6 weeks of definitive whole breast or chestwall irradiation at a dose

of 50.0 Gy with a 10-16 Gy boost).

- Patients will be between 6 months and 1-year post radiation treatment.
- Brief Fatigue Inventory (BFI) score of >25
- Satisfactory results of screening safety labs, urine pregnancy test and drug test.
- Ability to understand study procedures and to comply with them for the entire length of the study.
- Women of reproductive capability will be enrolled, but each woman needs to discuss with the study team the method of birth control used and if the method is reliable and effective method for her. If a woman becomes pregnant during the course of active study participation, she must agree prior to enrolling in the study that she will report the pregnancy to the study team. With a confirmed pregnancy, the subject will be dropped from the study. *indicate whether contraception is necessary and required*[KB3]. *If yes, include details of allowable contraception methods for trial*[ESA4].

Exclusion Criteria:
Candidates meeting any of the exclusion criteria at baseline will be excluded from study participation. Exclusion criteria for this study include:

- Inability to lay supine for one hour at a time, given the nature of the massage intervention.
- Based on ICD-10 proposed criteria, a diagnosis of CRF will require evidence from the history, physical exam, and laboratory findings that the fatigue is a consequence of cancer or cancer therapy and not primarily a consequence of comorbid psychiatric disorders (schizophrenia, depression, generalized anxiety disorder, bipolar disorder, dementia, delirium or OCD).
- Subjects who are actively suicidal or homicidal.
- Medical conditions felt to be clinically contributing to fatigue based on the investigator's history, physical examination, and assessment: anemia (hemoglobin less than 10 g/dl), hypothyroidism (thyroid stimulating hormone greater than 4.6 MCU/mL), uncontrolled pain, medical problems associated with fatigue: chronic obstructive pulmonary disease, congestive heart failure, renal disease, hepatic dysfunction, autoimmune disease, neurological disorders such as multiple sclerosis or Parkinson's disease, and sleep apnea.
- Medications felt to be clinically contributing to fatigue based on the investigator's history, physical examination, and assessment including: opioids, sedating anti-histamines, antidepressants, anxiolytics or neuroleptics
- Body-mass index less than 18.5 (kg/m^2)
- Treatment with corticosteroids or other immunosuppressants within the past 6 months
- Unable to comply with the protocol for any reason.
- Use of anti-inflammatory medications such as corticosteroids or other drugs known to affect the immune system will also be exclusionary as will the use of psychotropic medications including antidepressants and anti-anxiety agents.
- Use of non-steroidal anti-inflammatory drugs and aspirin is allowed but must be tracked.
- Other exclusion criteria include: illicit drug use, shift work, current dieting, excessive regular use of alcohol (more than two 5 ounce glasses of wine or equivalents/day) or a history of binge drinking (more than 7 drinks/24 hour period) within the last 6 months
- Subjects who have used massage as a therapeutic modality (medical or psychological) at any point in their lives for the treatment of medical conditions
- Subjects who have massages on a regular basis. Regular massage usage will be operationally defined as receiving 4 or more massages/year for the last 5 years.
- Subjects currently employing any other CAM manual therapy and/or holistic therapies to treat a perceived health problem. However, since past experience with CAM therapies should not confound any of the analyses of the experiments proposed in this study, we will not exclude individuals who have engaged in a CAM manual therapy in the past, nor will we exclude individuals who practice yoga or meditation for well-being, take vitamins or use nicotine.
- Adults over the age of 65 will be excluded from the study. This population tends to undergo changes in the physiological parameters we are evaluating. Therefore, inclusion of this population would skew various biological measures and this pilot investigation does not have a large enough sample size to

control for it[ESA5]..Older subjects could be included at the discretion of the PI.
- Specify health status or any clinical conditions (e.g., life expectancy, co-existing disease) or other characteristics that precludes appropriate diagnosis, treatment or followup in the trial.
- People unable to read and understand the informed consent document because of language difficulties.
-

- ***Non-English speakers***[KB6]
  - *Women who are pregnant or lactating*[KB7].
  - ***Women***[ESA8] ***using oral or implantable birth control will not be excluded from the study.*** *Women who become pregnant while enrolled will be discontinued from the study and will be instructed to exercise, which is the standard recommendation for cancer-related fatigue.*
  - Inability or unwillingness of individual to give written informed consent.

4.0 Subject Evaluation

Diagnostic & Symptomatic Measures[KB9]
Clinician rated:
- Brief Fatigue Inventory (BFI)
- Mini-International Neuropsychiatric Interview (MINI)
- Relaxation Condition Preference/Expectancy Scale

Self Report:
- Credibility/Expectancy Questionnaire (CEQ)
- Multidimensional Fatigue Inventory (MFI)
- Patient-Reported Outcome Measurement System (PROMIS[ESA10])

5.0 Study Enrollment Procedures

- Participants will be derived from several sources: 1) Most will be referred from the Radiation Oncology Follow-up Clinics at Emory University, 2) Women who respond to study advertisements or clinicaltrials.gov, or 3) Women referred from practitioners and on the Women' Mental Health Program (WMHP) website.
- Potential participants can call the **Women's Mental Health Program** Emory Department of Psychiatry research study phone at (404) 778-2497 any time. Messages left will be returned within 24-48 hours.
- A study screening log will be kept that documents study eligibility, reasons for exclusion of any subjects not randomized.
- A study enrollment log will be kept that documents subjects enrolled. Because the study is blind to the investigators a separate subject randomization log will be kept.
- A study consent will be signed by subjects who read, write and understand the English language at least at an 8th grade reading level, determined by comprehending the study consent, which is written at that reading level.
- Subjects who cannot consent for themselves will not be included in this study.
- Potential subjects will be given a sample copy of the consent to review at their leisure and will be encouraged to discuss the consent with family members or significant others. The consent process will be conducted at the screening visit by a study coordinator. The subject will be given the opportunity to ask the study coordinator questions and receive responses they understand prior to signing the consent. The principle investigator and/or other senior study team members are available for questions from the subject as well.
- The subject will be told that the study is voluntary, so participation in the study can stop at any time if the subject wishes.
- Subjects meeting study criteria will be randomized to one of three study groups.
- Approximately 72 survivors of breast cancer will be enrolled in this study (in order to have 60 complete, 20 per treatment group).
- We will use variable sized, permuted block randomization.

- We will stratify randomization within groups with severe vs. moderate baseline severity of fatigue, defined as a self-rating ≥7 on item 3 of the BFI at baseline (self-rating of worst level of fatigue during the past 24 hours, on a 0-10 scale).
- Information provided at screening: Full name, phone number, address, birth date, medications used in the past and present, medical history, diagnosis, and where they heard about the study.

6.0 Therapy

Massage: Swedish massage is the most commonly offered and best-known type of massage. The therapist uses non-aromatic massage oil to facilitate making long, smooth strokes over the body. Swedish massage is done with the subject covered by a sheet, a technique called "draping." One part of the body is uncovered, massaged, and then covered up before moving onto another part of the body. Primary techniques used in the research protocol therapy are: effleurage, petrissage, tapotement.

Light-Touch Protocol: The light-touch side of the research is based on the concept there will be a noticeable effect with regard to massage when compared to light-touch alone without the massage. The protocol followed will be the same as the massage protocol other than the therapist will work around the subject using light-touch only. The total session time is 45 min.

7.0 STUDY INTERVENTIONS

7.1 Interventions, Administration, and Duration [KB11]

- All treatment visits take place at Clinic B, Suite 6100, 1365 Clifton Rd., NE, Atlanta, GA 30322.
- Licensed massage therapists are assigned to perform the massage and light touch **therapy**therapies. These therapists are certified massage therapists from the accredited Atlanta School of Massage. Massage therapists are considered to be providing a commercial service and therefore not engaged in the research. The therapists will be routinely proctored by a member of the Medical Staff, Dr. Mark Rapaport or D. Jeffrey Newport. [ESA12]The message therapists complete group hands on training every 3-4 months in order to ensure the use of a standardized massage protocol throughout the duration of the study[ESA13].
- Subjects will participate in one study visit per week for treatment sessions 1-6. For detailed descriptions of the massage and light touch protocols see appendices 1 and 2. Both massage and light touch treatment sessions will be 45 minutes. In the Swedish massage, the therapist uses non-aromatic massage oil to facilitate making long, smooth strokes over the body. Swedish massage is done with the subject covered by a sheet, a technique called "draping." One part of the body is uncovered, massaged, and then covered up before moving onto another part of the body. The protocol followed will be the same as the Swedish massage other than the therapist will work around the subject using light touch only.

  The risks of this study's interventions to a participant are minimal; the magnitude of harm or discomfort is not greater than that encountered in daily life or through the performance of routine physical or psychological examinations or tests. One of the potential risks of this study is the possibility of experiencing side effects from massage such as muscle soreness, minor inflammation or bruising.
-
- If a subject experiences discomfort secondary to skin sensitivity or scarring that area will not be touched by the therapist in the future and we will not this in the case report form.
- ***Include instructions for modifications to the study interventions, if appropriate and clearly explain modification: Include directions for modification of SMT or LT due to injury, surgery, hair, etc*[ESA14]...**

7.2 Handling of Study Interventions [KB15]

- See appendix 1 and 2 for detailed descriptions of the Swedish massage and Light touch therapies.
- See appendix 3 for the long and short versions of the therapist's script.

- Randomization lists for treatment assignment will be generated by the Biostatistics group at Emory, who have no connection to study subjects or data. During the course of the study, only the study coordinator, therapists and the subjects will be unblinded to delivery of SMT vs. LT treatment intervention; these individuals will not be involved in endpoint assessment, which will be obtained by subject self-report measures of fatigue. The study coordinator will not have access to the study database[ESA16]. Study therapists will input their own notes about each session into a separate database that will not be transferred to the study statistician until after initial analyses of the primary aim of the study have been carried out using blinded treatment codes. We will continue to follow a strict policy of avoiding mention of treatment assignment (by the study coordinator or therapists) during weekly staff meetings to discuss issues related to the conduct of the study.

7.3 Concomitant Interventions [KB17]

7.3.1 Allowed Interventions

- non-steroidal anti-inflammatory drugs and aspirin – allowed but must be tracked.
- yoga or meditation for well-being – allowed but must be tracked.
- vitamins – subjects will be instructed to maintain the same level of intake throughout the study
- nicotine – subjects will be instructed to maintain the same level of intake throughout the study
- caffeine – subjects will be instructed to maintain the same level of intake throughout the study
- moderate exercise – subjects will be instructed to maintain the same level of exercise throughout the study
- oral or implantable birth control.

7.3.2 Required Interventions [KB18]

- none

7.3.3 Prohibited Interventions (include list in appendix?)

- Medications felt clinically to contribute to fatigue including:
  - Opioids
  - sedating anti-histamines
  - antidepressants
  - anxiolytics
  - neuroleptics
- Corticosteroids or other immunosuppressants
- anti-inflammatory medications such as corticosteroids or other drugs known to affect the immune system
- Illicit drugs
- dieting
- excessive alcohol (more than two 5 ounce glasses of wine or equivalents/day)
- massage (medical or psychological)
- any other CAM manual therapy and/or holistic therapies to treat a perceived health problem

7.3.4 Adherence Assessment [KB19]

Adherence for this study is defined as receiving at least 5 out of six possible intervention session. The study window for each intervention is 7 days plus or minus 3 **Adherence**days. Adherence to the protocol is monitored via audiotape, therapists notes, study participant **to**query. The therapists undergo regular reliability training to ensure that they have not drifted from the proscribed protocol.

a study regimen is generally defined as the extent to which participants take medications or comply with other study requirements as prescribed by the investigators. Define adherence (e.g., at least 80% of treatment intervention pills taken, 85% of exercise sessions attended). Provide details as to how adherence to study intervention will be assessed (e.g., pill counts, electronic monitoring devices, attendance at counseling sessions) and in the section on Data Analyses (Section 9.5), describe how this information will be incorporated into the analysis of the study results.

Not Applicable

8.0 Study Procedures

8.1 Schedule of Evaluations

Treatment Session	Screen	Tx0	Tx1	Tx2	Tx3	Tx4	Tx5	Tx6
Week # for Groups 1 & 2	**0**	-	**1**	**2**	**3**	**4**	**5**	**6**
Week # for Group 3[a]	**0**	**1**	**7**	**8**	**9**	**10**	**11**	**12**
Brief Fatigue Inventory (BFI)	X							
Medical History & Physical Exam	X							
MINI Psychiatric Exam	X							
Urine Toxicology, Pregnancy & Safety labs	X							
Preference / Expectancy (of Relief from Symptoms of Fatigue) Scale	X							
Multidimensional Fatigue Inventory (MFI)		X[B]	X[c]		X			X
Research Bloods		X[B]	X[c]		X			X
Credibility / Expectancy Questionnaire (of Relief from Symptoms of Fatigue)		X[B]	X[c]					
PROMIS Fatigue Measure		X[B]	X[c]					X
Safety Assessments		X[B]	X	X	X	X	X	X

[a]For Group #3, events listed for Tx1-Tx6 visits occur during weeks 7-12, in addition to a Tx0 visit with no treatment.
[B]Tx0 is Group #3 (6 week wait, followed by randomization to massage or light touch therapy) only.
[c]At Tx1 visit, collected prior to Massage or Light Touch intervention; at other visits, collected after intervention.

8.2 Description of Evaluations

8.2.1 Screening Evaluation[KB20]

8.2.2 Phone screen

8.2.3 Screen[KB21]

- Describe enrollment of subject at beginning of in person screen.
- A screening visit will take place either at the Radiation Oncology Follow-up Clinics at Emory University or in the Women's Mental Health Program, Suite 6100 Clinic B where subjects will be asked to undergo a Brief Fatigue Inventory (**BFI**), the Mini-International Neuropsychiatric Interview (**MINI**).
- The subjects will have the study conditions explained to them in a neutral manner, will fill out the Expectancy of Relaxation Scale and the Relaxation Condition Preference Scale.
- Screening blood and urine samples will also be collected to asses a subject's overall health status.

8.2.4 Randomization and Baseline

- All treatment visits take place at Clinic B, Suite 6100, 1365 Clifton Rd., NE, Atlanta, GA 30322.
- Randomization
  - If a subject is eligible, she will be randomized to one of three treatment groups:
    - 1) Massage therapy once per week for 6 weeks,
    - 2) Light touch therapy once per week for 6 weeks, or
    - 3) A 6 week wait, followed by randomization to massage therapy or light touch therapy once per week for 6 weeks.
  - R**Specify time window for (a) randomization relative to completion of screening and baseline and (b) initiation of study intervention relative to randomization.**[KB22]andomization occurs within 7 days (plus or minus 3 days) of the screening visit, at the time of the first intervention session.
- Baseline (Treatment Visits 0 and 1)

- All subjects (Groups 1, 2, 3) will attend the first weekly session. At the first session, immediately after each subject is randomized and informed of their treatment group assignment, each subject will complete:
  - Safety Assessments[KB23]
  - MFI
  - Credibility/Expectancy Questionnaire
  - PROMIS
  - Research blood sample drawn.
- Subjects assigned to Groups 1 and 2 will then have their first treatment sessions (Tx1) and subjects assigned to Group 3 (Tx0) will leave.
- At week 7, Group 3 will begin SMT or LT and will follow the procedures described for Groups 1 or 2 during Tx1-6

8.2.5 Treatment Visits

- Treatment visits 2, 4 and 5
  - Safety Assessments
- Treatment Visit 3
  - Safety Assessments
  - MFI
  - Research blood draw
- Treatment Visit 6
  - Safety Assessments
  - MFI
  - PROMIS
  - Research blood draw

8.2.6 Blinding

For blinded studies, describe blinding and unblinding methods. Address the following points:

- *Procedure for retaining the blind (including specific procedures for protecting the blind should data collected in the study offer evidence of a participant's assignment to a particular study arm)*
- *Individual authorized to break the blind*
- *Circumstances for breaking the blind*
- *Procedure for breaking the blind.* [KB24]

At each of the 7 study visits (screening visit and 6 treatment visits), employing a standardized form, the study coordinator will ask each subject about life stressors, exercise levels, medical health, medication use and illicit substance use over the past week. Study groups 1 and 2 a research blood sample (20 ml) will be obtained from subjects at baseline at the beginning of the first treatment visit (Tx1), and again after the third (Tx3) and sixth (Tx6) treatment visits. Study group 3, will have a research blood samples (20ml) obtained at visits Tx0, Tx1, Tx3 and Tx6. Over the course of the study, 80ml of blood will be collected.

In this study, the light touch therapy is considered the control arm because we have demonstrated in our previous and current NCCAM-funded studies that light touch does not significantly decrease or increase ratings of depression or anxiety and does not seem to down-regulate plasma and salivary cortisol. However, based on results of our recently completed NCCAM-funded study, we have demonstrated this to be an active-control treatment, rather than a placebo.

Sessions will be monitored by digital recorder and 10% of the recordings will be randomly audited for protocol integrity. Subjects will be interviewed by the research coordinator at the end of each visit to review the subject's perception of the experience and any variations from expected procedures. All ratings will be checked for completeness prior to the subject leaving. We have standardized SOPs for all aspects of the protocol from initial subject screening, to procedures for standardized intervention visits, blood sample collection and processing, and data recording and management.

Subjects will be provided up to $400 for their participation in this study. Subjects will accrue $40 for completing treatment visits 0, 1, 2, 4 and 5, and $100 for completing treatment visits 3 and 6. Subjects that do not finish the study, will be paid for the visits they have completed. If subjects complete all study visits, they will receive $360 total if assigned to study groups 1 or 2, and $400 total assigned to study group 3. Actual payment will be made one time via check issued when a subject's participation is completed. However, the payment accrual structure will be progressive to enhance retention. Subjects may be reimbursed for their parking costs that result from being in this research study.

9.0 Data Collection

All clinical information will be coded using a HIPAA compliant identifier. Psychometric and biological data will be stored in REDCAP. Database features include point-of-entry integrity checking, automated report generation, and automated data export to statistical and graphics software.

10.0 Statistical Considerations[KB25]

10.1 General Design Issues

State the statistical hypotheses.

Describe the reasons for choice of study design (e.g., parallel groups, crossover, immediate versus deferred intervention, factorial, large simple trial, equivalency or non-inferiority trial); why certain design features were chosen (e.g., for a crossover trial, how the length of the washout period was chosen).

Describe the primary and secondary hypotheses and the primary and secondary outcome measures as well as their validity and reliability.

10.2 Sample Size and Randomization

Describe sample size calculation and effect size with respect to power. Specify the test statistic; Type I and Type II error rates; assumed event rate event rate for dichotomous outcome (mean and / or variance for continuous outcome) for each study arm; assumed rates of drop-out, withdrawal, cross-over to other study arms, missing data, etc.; and approach to handling withdrawals and protocol violations, in terms of an "intent to treat" approach.

Treatment Assignment Procedures

Describe the treatment assignment procedures (randomization, minimization, relevant criteria, etc). If such procedures are proposed describe rationale as well as the procedure.

Plans for the maintenance of trial randomization codes and maintaining appropriate masking for the study should be discussed, including the timing and procedures for planned and unplanned breaking of randomization codes should be included.

For blinded studies, describe blinding and unblinding methods. Address the following points:

- *Procedure for retaining the blind (including specific procedures for protecting the blind should data collected in the study offer evidence of a participant's assignment to a particular study arm)*
- *Individual authorized to break the blind*
- *Circumstances for breaking the blind*
- *Procedure for breaking the blind*

If the randomization will be stratified, indicate whether (and why) there is a sample size goal for each stratum. Identify what factors (if any) will be used to stratify the randomization.

10.3 Definition of Populations

Define ITT (Intent to treat) and per protocol populations for analyses.

10.4 Interim Analyses and Stopping Rules

If an interim analysis is planned, describe the rationale, effect on "spending" the Type I error, and method for adjusting calculations. As relevant, provide guidelines for stopping the study for reasons of efficacy, safety, futility, or poor study performance (e.g., slow accrual, high losses-to-followup, and poor quality control).

Describe safety findings and statistical rules that would temporarily suspend enrollment and/or study intervention until a safety review is convened (either routine or ad hoc) to determine whether the study should continue per protocol, proceed with caution, be further investigated, be discontinued, or be modified and then proceed.

Examples of findings that might trigger a safety review are the number of SAEs overall, the number of occurrences of a particular type of SAE, severe AEs/reactions, or increased frequency of events. Such findings are presented to the study statistician or to the Independent Monitoring Committee (IMC) statistician to review the events by group to determine whether there are statistical as well as clinical concerns. The statistician reports his findings to a closed session of the IMC or to the Safety Officer and/or NCCAM. The findings are used to determine what steps will be taken.

10.5 Outcomes

Discuss how the outcomes will be analyzed. Describe whether the documentation of an outcome will be reviewed and adjudicated by a committee, how quickly the committee will perform the adjudication, and whether the committee will be masked to the participant's intervention group assignment.

10.5.1 Primary Outcome

State and define the primary outcome measure and specify at which study visit the outcome assessments will be performed.

10.5.2 Secondary Outcomes

State and define the secondary outcome measures.

10.6 Data Analyses

Describe the descriptive and inferential statistical methods that will be used to analyze the outcomes and other study data. Specify any confounding variables for which it is anticipated adjustment will be made.

In accordance with NIH policy, if data from prior studies do not negate strongly the existence of significant differences of clinical or public health importance in the intervention effect between gender and racial/ethnic subgroups, a statement should be included noting that a valid analysis of the intervention effect will be performed in these subgroups. If data from prior studies do not strongly support the existence of significant differences in the intervention effect between subgroups, then the analyses need not have high statistical power for detecting clinically meaningful differences.

11. DATA COLLECTION AND QUALITY ASSURANCE

11.1 Data Collection Forms

Indicate how information will be collected for each participant and by whom. For example if a blinded observer will perform outcome assessments, state who this person will be. Describe methods for maintaining confidentiality of participant records. Identify any data that will be recorded directly on the CRFs (i.e. no prior written or electronic record of data) as this will be considered source data. (ICH Guidelines, E6.4.9)

11.2 Data Management

Briefly describe clinical site responsibilities in data collection and management.

Briefly describe Coordinating Center (or Data Management/Statistical Center) responsibilities in data management.

Briefly describe data collection forms.

11.3 Quality Assurance

11.3.1 Training

Describe types and mechanisms of training of staff for the study.

11.3.2 Quality Control Committee

If there is a study quality control committee, describe membership and list the reports that they review.

11.3.3 Metrics

Provide quality control metrics for outcome measures.

11.3.4 Protocol Deviations

Describe how protocol deviations will be captured, documented, and reviewed.

11.3.5 Monitoring

Briefly describe methods (e.g., site monitoring) for assuring protocol compliance, and data quality at the clinical sites, including review of records, consent forms, etc. The types of materials to be reviewed; who is responsible, and the schedule for reviews may be specified or referenced in the Manual of Procedures (MOP).

12.0 Adverse event reporting

All serious adverse events will be documented and reported immediately to the Emory IRB, the DSMB, and NCCAM/NCI. All AEs will be noted and recorded with required documentation and reviewed by the Emory IRB, the DSMB, and NCCAM/NCI in a summary report submitted annually.

13.0 Data and safety monitoring plan (DSMP)

A Data and Safety Monitoring Board (DSMB) will be convened as an independent body charged with ensuring that the safety of study subjects is protected and that the scientific goals of the study are being met. A preliminary charter for this project's DSMB can be found on the following pages.

Charter of the DSMB

Composition of the DSMB

The DSMB Committee will consist of permanent members from the Clinical Research Oversight Committee and ad-hoc members from the Department of Psychiatry and Behavioral Sciences and the Department of Neurology as needed to review reports. The permanent members include the co-chairs, Boadie Dunlop, M.D., and Larry Tune, M.D., along with Bobbi Woolwine, LCSW (Ms Woolwine is a member of the study staff and will be recused from all DSMB discussions of this study), Marion Evatt, M.D. and Tanja Mletzko-Crowe, M.A. They have agreed to serve as the DSMB for clinical studies conducted by Emory researchers in the Department of Psychiatry & Behavioral Sciences that the Emory Institutional Review Board has determined to require DSMB review. Given the nature of the research under the authority of this DSMB, the Committee does not have a sitting statistician as a member. However, a statistician will be consulted whenever the committee believes such a statistical analysis is necessary to determine significant issues around safety of any research intervention. Valerie Cruz serves as the DSMB's administrative assistant.

Bobbi Woolwine is a member of this study's staff and she will be recused from all DSMB discussions of this study.

Organization of DSMB Meetings

The DSMB will conduct open monthly meetings in a location convenient to committee members. The DSMB may close the meeting for discussion of studies at the co-chairs' discretion.

Responsibilities and Roles of the DSMB

The primary aims of the DSMB are to contribute to the protection of research participants and to assist and advise Principal Investigators in their efforts to limit risks from research participation.
The specific roles the DSMB aim to fulfill include the following:

1. To monitor recruitment figures and losses to follow-up.
2. To monitor research data for evidence of treatment harm or violations of confidentiality.
3. To decide whether to recommend that a research study continue to recruit participants, or whether recruitment should be halted or otherwise curtailed.
4. To advise on protocol questions and deviations when requested by the study investigators.
5. To monitor compliance with previous DSMB recommendations.

Submission of Reports to the DSMB

A) *Initial Submission*

At the time of submission of a new research study to the Emory IRB, the PI should submit a copy of the protocol to the DSMB, if the PI expects that the study will require the use of the Department of Psychiatry DSMB. If the PI does not expect to require a DSMB, but then is informed by the IRB after initial IRB review that a DSMB is required, the PI should submit the protocol to the DSMB as soon as possible.

B) Subsequent Submissions

PIs should keep in mind that Emory IRB continuing review approval is often contingent upon the DSMB review of data for the most recent reporting period. At least two weeks prior to each DSMB

meeting, the study principal investigator (PI), or his or her designee, will prepare a report to be reviewed during that meeting. The report will follow the template for reporting, which is available from Ms. Cruz.
Data required for the report include the following:

1. The most recent IRB-approved version of the informed consent form, or most recent draft if the study does not yet have IRB approval.
2. A summary of the study protocol.
3. The total number of participants who have signed consent for the study.
4. The total number of participants randomized (if applicable)
5. The number of participants terminating early from the study, with a tally of the reasons for these early terminations.
6. The number of serious adverse events that have occurred, with a summary report of each event and its resolution.

   A serious adverse event is defined as: "Any adverse experience occurring that results in any of the following outcomes: death, a life-threatening adverse experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect."
7. A summary of all adverse events occurring over the course of the study.
8. Copies of all Reportable Events submitted to the IRB.

   The PI should notify the DSMB of any and all actions taken by the IRB in response to reportable events.
9. A summary and explanation of any breaches of participant confidentiality that have occurred during the study.
10. A summary of any new research findings by the PI or others that may alter the safety/adverse event profile of the intervention being studied (e.g. newly published studies).

All data will be presented to the DSMB in a manner to maintain patient confidentiality whenever possible.

C) *Submissions of Serious Adverse Events and Reportable Events*

All Serious Adverse Events and IRB-defined Reportable Events should be reported to the DSMB within ten days of their occurrence.

Review Procedures

Upon receipt of a report to the DSMB, one of the DSMB co-chairs will assess whether the report requires a full DSMB review, or whether an expedited review can be performed. Expedited reviews will be reviewed only by one of the co-chairs. Criteria for a report to receive expedited review include ALL of the following:
Criteria for Expedited Review:

1. Absence of any SAEs or Reportable Events during the most recent reporting period.
2. Absence of any adverse event that was not expected (i.e. explained in the informed consent form or identified in the protocol.
3. Absence of any significant violations of patient confidentiality. The DSMB will review each research protocol and plans for data and safety monitoring once per year (or every 6 months if the protocol is considered 'high risk' by the IRB).

The DSMB as a general rule does not ask for unblinded data from ongoing studies. However, in some cases it may ask for unblinded data if the Committee believes safety concerns warrant such an analysis.

Upon completing the review, the DSMB will issue a report that summarizes the following:

All serious and unexpected adverse events or other unanticipated problems that involve risk to study participants, and whether these appear related to the study-based interventions or research assessment protocols. Reports will not specifically disclose the treatment arm of the study unless this disclosure is required for safety reasons.

Possible recommendations to the IRB and PI from the DSMB review include:

1. No action necessary; study may continue to enroll.

2. Stopping the study, or a single arm of the study
3. Proposing protocol changes

There will be ongoing communication between the PI, the Emory IRB, and the DSMB as required. The effective functioning of the DSMB depends completely upon the full and timely reporting by the PI of safety-related concerns.

Statistical consultation will be provided on an as needed basis by the Division of Biostatistics. The PI will be responsible for any charges resulting from additional review requirements.

Management of Potential Competing Interests of DSMB Members

To avoid perception that members of the DSMB may be biased in some fashion, it is important for the credibility of the decisions made by the DSMB and the integrity of the trial that Committee members recuse themselves from review of a study if any of the following apply:

1. An active contributor to the research study under review.
2. Significant stock ownership in any commercial companies involved (>$10,000).
3. Consulting arrangements with the sponsor of a research study.

Study Review Criteria / Stopping Rules and Guidelines

Guidance for the conduct of safety, and guidelines / stopping rules and protocol modification will be established prior to the DSMB's first evaluation of data.

Safety Analyses

The primary safety endpoints are the assessment of the subjects' health by review of the AE and SAE data which will be collected at every study visit, and by telephone follow-up for missed visits.

Stopping Guidelines / Stopping Rules: Safety

The DSMB may recommend termination or modification of the study if there is any evidence that the study procedures negatively and seriously affect study subjects, without interim analyses. Should the Board recommend termination of the trial, a full vote of the Board will be required.

Effectiveness Analyses

There is no plan to perform interim effectiveness analyses.

Reports

Monitoring for Safety

Formal DSMB safety reviews will occur at least annually.

Definition of Adverse Event

Any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research. The severity of Adverse Events will be graded using the National Cancer Institute's Common Terminology Criteria for Adverse Events:

Grade 1 Mild AE
Grade 2 Moderate AE (interferes with some function but not day-to-day activities)
Grade 3 Severe AE (interferes with activity and daily living)
Grade 4 Life-threatening or disabling AE
Grade 5 Death related to AE

The DSMB will monitor the study for any adverse events that arise over the course of the project, however, the following adverse events have been identified by the co-PIs as events that are likely to occur during the course of the trial:

1) Psychological and/or emotional discomfort arising from the clinical interview and questionnaires
2) Blood draw complications
3) Myalgias (muscle inflammation) and bruising from massage

Definition Serious Adverse Event

A serious adverse event is defined as any fatal event, immediately life-threatening event, permanently or substantially disabling event, event requiring or prolonging inpatient hospitalization, or any congenital anomaly. This also includes any event that a study investigator judges to impose a significant hazard, contraindication, side effect, or precaution.

Monitoring for Effectiveness

The DSMB will not monitor effectiveness outcomes to determine relative risk/benefit, futility, or for early termination due to overwhelming effectiveness in this R21.

Monitoring for Study Conduct

The DSMB will review data related to study conduct. Data to be reviewed and listed in the DSMB reports includes but is not limited to: enrollment rates over time, summary of protocol violations, and completeness of treatment and follow-up visit data.

Data Flow for Adverse Events

The DSMB will carefully monitor adverse events annually throughout the duration of the study. All SAEs will be reported to the local IRB, regardless of any judgment of their relatedness to the study drug, within 48 hours of their occurrence. All relevant information will be reported to the IRB for each SAE including information about the event and its outcome, the subject's medical history and current conditions, and all relevant laboratory data. Additional reporting to the funding agency, NCCAM, as well as the DSMB will be done within 48 hours of notifying the IRB.

For an SAE, the DSMB will convene to review all information about the event and disclose their findings in a report to be issued within 10 days of being notified of the event.

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15. SUPPLEMENTS/APPENDICES

- Appendix 1 – Detailed description of the Swedish massage protocol
- Appendix 2 – Detailed description of the Light touch protocol
- Appendix 3 – Massage therapist script
- List of exclusionary drugs
- List of drugs not allowed during the protocol