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Design and methods of a multi-site, multi-behavioral treatment trial for menopausal symptoms: The MsFLASH experience ☆

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ABSTRACT

Background: Behavioral strategies are recommended for menopausal symptoms, but little evidence exists regarding efficacy.
Purpose: Describe design and methodology of a randomized controlled 3 by 2 factorial trial of yoga, exercise and omega-3 fatty acids.
Methods: Women from three geographic areas with a weekly average of ≥14 hot flashes/night sweats, who met exclusion/inclusion criteria, were randomized to 12 weeks of: 1) yoga classes and daily home practice; 2) supervised, facility-based aerobic exercise training; or 3) usual activity. Women in each arm were further randomized to either omega-3 supplement or placebo. Standardized training, on-going monitoring, and site visits were adopted to ensure consistency across sites and fidelity to the intervention. Participant adherence to the intervention protocol was monitored continuously, and retention was actively encouraged by staff. Information on adverse events was systematically collected.
Results: Of 7377 women who responded to mass mailings, 355 (4.8%) were randomized; mean age was 54.7 (sd = 3.7), 26.2% were African American, 81.7% were post-menopausal, and mean baseline frequency of daily hot flashes/night sweats was 7.6 (sd = 3.8). Adherence of ≥80% was 59% for yoga, 77% for exercise training, and 80% for study pills. Final week 12 data were collected from 95.2%
Conclusions: Conducting a multi-site, multi-behavioral randomized trial for menopausal symptoms is challenging but feasible. Benefits included cost-effective study design, centralized recruitment, and methodologic standardization.

1. Introduction

Over 38 million U.S. women will transition from pre- to post-menopause during the next decade, and 30–80% of these women will experience hot flashes/night sweats,

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collectively referred to as vasomotor symptoms (VMS) [1]. About 10% consider their symptoms severe [1], 44–82% report that VMS interfere with sleep, mood, and daily functioning [2], and about 60% seek medical advice and treatment for relief of menopausal symptoms [3]. For many years, hormone therapy (HT, either estrogen plus progesterone, or estrogen alone for women without a uterus) was the standard of care and was generally effective for reducing the frequency and severity of hot flashes/night sweats. However, findings from the Women's Health Initiative (WHI) published in 2002 [4] showed an increase in the risk of breast cancer, thromboembolism, myocardial infarction, stroke, gall bladder disease, and dementia in women randomized to combined HT (estrogen and progesterone). Subsequently, HT use declined dramatically [5,6], and the on-going search for safe and effective alternative treatments took on added urgency.

To encourage that search, the National Institutes of Health awarded funding in 2008 to the MsFLASH (Menopause Strategies: Finding Lasting Answers for Symptoms and Health) Research Network to conduct a series of randomized controlled trials of innovative treatments for VMS. The MsFLASH Network is a collaborative project that includes a data coordinating center (DCC), located at the Fred Hutchison Cancer Research Center in Seattle, five clinical sites, located at the Group Health Research Institute in Seattle, Kaiser Permanente Northern California in Oakland, Indiana University in Indianapolis, University of Pennsylvania Medical School in Philadelphia, and the Massachusetts General Hospital/Harvard University in Boston, and NIH program officers from the National Institute on Aging (NIA), the Eunice Kennedy Shriver National Institute of Child Health and Development (NICHD), the National Center for Complementary and Alternative Medicine (NCCAM), and the Office of Research on Women's Health (ORWH). The MsFLASH investigators have already published positive results from the first trial, which tested the efficacy of escitalopram vs. placebo [7]. A second trial, known as Interventions for Menopausal Symptoms: the 3 by 2 Factorial Design Examining Yoga, Exercise and Omega-3 Supplementation, has recently been completed and primary results of that trial are expected shortly in a series of three published manuscripts. This trial was designed specifically to test the efficacy of a low risk nutritional supplement and two behavioral interventions, which many patients prefer as initial treatment options. The purpose of the current report is to describe the rationale for the 3 by 2 study design, to discuss issues relevant to intervention-specific methodology and implementation, and to present data on recruitment, eligibility, and baseline characteristics. We highlight issues faced in the implementation of this complex and challenging multi-behavioral, multi-site protocol.

2. Methods

2.1. Overview of study design

This study was a 12-week, randomized controlled, 3 by 2 factorial trial that evaluated the following interventions: yoga, aerobic exercise, and omega-3 fish oil supplementation. With this design, 30% of the women were randomized to yoga, 30% to exercise, and 40% to usual care. Within each of these groups, women were further randomized in a 1:1 ratio to active omega-3 supplementation capsules or matching placebo capsules three times a day. The primary aims of the trial were to compare changes in self-reported frequency, and bother of vasomotor symptoms in each specific intervention arm to those in the control group.

The sample size of each cell provided 90% statistical power to test hypotheses related to the efficacy of each intervention vs. placebo/usual activity on the primary outcomes of VMS frequency and bother. For each intervention, a Type I error rate of 2.5% was assumed to control for testing of two primary outcomes. The study did not provide sufficient power to detect small or moderate differences in efficacy between yoga and exercise, or to accurately estimate potential additive effects of the behavioral interventions and omega-3, both of which would have required a much larger sample. Nevertheless, those hypotheses can be explored in secondary analyses in a more rigorous fashion through the 3 by 2 factorial design than would be permitted by separate trials of each intervention.

Fig. 1 summarizes the basic design of the study. Briefly, following telephone screening of responders to mass mailings, women completed two weeks of a daily hot flash diary and a baseline questionnaire. They then attended a clinic examination that included a blood draw, blood pressure and body size measurements, and a graded exercise treadmill test. A week later, after completing an additional one-week hot flash diary, questionnaires that included items on outcome expectancy, one week of monitoring for sleep (actigraphy and diary) and usual activity (pedometry), and collection of saliva samples for cortisol measurement four times a day on two consecutive days, women returned to the clinic for randomization and a measure of heart rate variability. An interim 7-day hot flash diary was completed during week 6, and a final diary in week 12, the last week of the intervention period. At the end of Week 12, women returned to the clinic where baseline measurements were repeated.

2.2. Rationale for selected interventions

Testing the efficacy of behavioral and complementary and alternative medicine (CAM) treatments was a priority for the MsFLASH Network because these treatments are widely available, acceptable, low risk, and provide many additional health benefits. The rationale for each intervention was based on existing evidence and potential biological mechanisms of efficacy. In the case of exercise, conflicting results from both observational studies and intervention trials suggested the need for a rigorous, adequately powered randomized trial [8]. The evidence for the efficacy of yoga as a treatment for VMS was based on the results of several prior studies that also indicated that yoga practice contributed to positive changes in total menopausal symptoms, psychological symptoms, sleep, and quality of life [9–12]. Hypothesized mechanisms for the efficacy of yoga included positive changes in stress reactivity and the balance of sympathetic to parasympathetic output [13]. Physiological adaptations to exercise training, including decreased resting heart [14] and improved heart rate variability [15,16] suggested similar biological mechanisms might apply to that intervention as