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Effects of Pharmacologic and Non-pharmacologic Interventions on Menopause-related Quality of Life: A Pooled Analysis of Individual Participant Data from Four MsFLASH Trials

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Abstract

Objective: The Menopause Strategies: Finding Lasting Answers for Symptoms and Health network conducted three randomized clinical trials (RCTs) testing six interventions treating vasomotor symptoms (VMS), and also collected menopause-related quality of life (QOL) measures. A fourth RCT assessed an intervention for insomnia symptoms among women with VMS. We describe these seven interventions' effects on menopause-related QOL relative to control in women with VMS.

Methods: We pooled individual-level data from 1005 peri- and postmenopausal women with ≥14 VMS/week across the four RCTs. Interventions included escitalopram 10–20mg/day; yoga/aerobic exercise; 1.8 g/day omega-3-fatty acids; oral 17-beta-estradiol 0.5 mg/day; venlafaxine XR 75 mg/day; and cognitive behavioral therapy for insomnia (CBT-I). Outcomes measures were the Menopause-related Quality of Life scale (MENQOL) and its subscales.

Results: Significant improvements in total MENQOL from baseline were observed with estradiol, escitalopram, CBT-I, and yoga, with mean decreases of 0.3 to 0.5 points relative to

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control. The largest improvement in the vasomotor subscale was observed with estradiol (−1.2 points), with more modest but significant effects seen with escitalopram, yoga and CBT-I. Significant improvements in the psychosocial subscale were observed for escitalopram, venlafaxine, and CBT-I. For the physical subscale, the greatest improvement was observed for CBT-I and exercise, while for the sexual subscale, the greatest improvement was observed for CBT-I, with yoga and estradiol demonstrating smaller effects.

Conclusions: These results suggest that for menopause-related QOL, women have a variety of treatment strategies to choose from and can select an approach based on most bothersome symptoms and individual preferences.

Keywords

quality of life; menopause; vasomotor symptoms

INTRODUCTION

Vasomotor and other symptoms associated with the menopausal transition (VMS) can adversely affect sleep, mood, pain, concentration, and energy levels, with associated negative effects on work, social activity, leisure activity, and sexual activity.[1] These menopause related symptoms have been demonstrated to influence health-related quality of life (Avis)[2]; as a result, menopause-related quality of life is an important outcome when assessing the impact of any treatment for menopausal symptoms.[3]

Low dose estrogen formulations have been shown to be effective for treatment of VMS and to improve quality of life[4]; however, many women cannot or prefer not to use hormone treatments. Thus, alternative pharmacologic and behavioral therapies are of interest to menopausal women and their providers. Comparison of the effects of the various suggested treatments for VMS on health-related quality of life would be informative for patients and clinicians when considering treatment options.

The MsFLASH (Menopausal Strategies: Finding Lasting Answers for Symptoms and Health) clinical trials network has conducted four randomized clinical trials with healthy menopausal women experiencing bothersome hot flashes. In total, these trials tested interventions in 1005 women, including a selective serotonin reuptake inhibitor (SSRI), a serotonin norepinephrine update inhibitor (SNRI), oral low-dose estrogen, yoga, exercise, omega-3 fatty acid supplementation, and cognitive behavioral therapy for insomnia (CBT-I); all measured menopause-related quality of life as a secondary outcome. The first three of these trials (MsFLASH 01–03)[5–10] targeted treatment of hot flashes as the primary outcome; the fourth trial (MsFLASH 04)[11] enrolled women with both moderately severe insomnia symptoms and bothersome hot flashes; in that trial, improving sleep was the primary treatment goal.

Before the first trial was launched, MsFLASH investigators developed network standards for study design, eligiblity and exclusion criteria, and study measures[12], with the intention that estimates of each intervention effect could be compared across trials and thus provide insight into their relative efficacy. To evaluate intervention effects on menopause-related quality of

life, the Menopause-Specific Quality of Life Questionnaire (MENQOL) was chosen for use in the MsFLASH trials due to the breadth of its domains, psychometric properties, brevity, and sensitivity to change over time.

Despite standardized MsFLASH methodology, there were some design differences between studies that need to be accounted for when examining intervention effects. We have previously published a novel joint comparative effectiveness analysis to examine the effects of the MsFLASH 01–03 interventions on VMS frequency and bothersomeness, using individual-level data and adjusting for differences between studies.[13] Using a similar approach, we have also reported data from four MsFLASH studies to compare the magnitude of treatment effects of multiple interventions on insomnia symptoms among women with significant insomnia symptoms.[14] The current paper applies a similar analytic approach to data from the same four MsFLASH trials in order to describe the magnitude of effects of seven interventions on menopause-related quality of life.

METHODS

Overview of MsFLASH trial designs

MsFLASH 01 was a randomized, placebo-controlled double-blind clinical trial designed to determine the efficacy and tolerability of 10–20 mg/day of the SSRI escitalopram for reducing VMS frequency and severity compared with placebo.[6,8] Participants were randomized in a 1:1 ratio to receive escitalopram 10mg/day or a matching placebo capsule for 8 weeks. If a woman did not report a reduction in VMS frequency of ≥50% or a decrease in VMS severity after 4 treatment weeks, her study medication dose was increased to 20 mg/day (or matched placebo) without unblinding the randomization.

MsFLASH 02 used a 3×2 factorial, randomized controlled trial design to compare the effects of yoga and exercise separately to a usual activity control group, and simultaneously to compare omega-3 fatty acid capsules to placebo capsules on VMS frequency and bothersomeness. Eligible women were randomized in a 3:3:4 ratio to 12 weeks of yoga, exercise, or usual activity, and simultaneously in a 1:1 ratio to 1.8g/day of omega-3 fish oil capsules or placebo capsules.[5,9,10,15] The 615 mg omega-3 fatty acids supplements were taken three times/day for 12 weeks and contained 425 mg eicospentanoic acid, 100mg docosahexaenoic acid, and 90 mg of other omega-3s.

MsFLASH 03 was a randomized, placebo-controlled double-blind, 8-week trial comparing the efficacy for reducing VMS frequency of low-dose oral 17-beta-estradiol 0.5 mg/day, the SNRI venlafaxine XR (37.5 mg/day for the first week, then 75 mg/day), or placebo in a 2:2:3 ratio.[7]

MsFLASH 04 was a placebo-controlled trial in which women with both hot flashes and insomnia symptoms were randomized to either telephone-delivered CBT-I or menopause education control. This was the only MsFLASH trial that focused specifically on treatment of insomnia symptoms rather than VMS, but VMS and other outcomes comparable to those collected in the other MsFLASH trials were measured.[11]

Design differences between the trials are described in Table 1. For all studies, randomization was accomplished through a secure Web-based database, maintained by the Data Coordinating Center, utilizing a dynamic randomization algorithm. The randomization was stratified by clinical site and race for MsFLASH 01 and by clinical site only for MsFLASH 02 and 03. MsFLASH 04 was conducted at one clinical site. The analyses presented here were not pre-specified in study protocols, but the MsFLASH studies were designed to permit eventual pooled analyses. All MsFLASH studies were approved by the Institutional Review Board of each clinical site and the Data Coordinating Center. All participants provided written informed consent.

Setting and participants

Participants were recruited from July 2009 to August 2015, primarily by mass mailing to age-eligible women using purchased mailing lists and health-plan enrollment files. There were five MsFLASH network sites (Boston, Indianapolis, Oakland, Philadelphia, and Seattle). All sites participated in at least two trials and each trial was implemented at three or four sites, except MsFLASH 04 which was implemented only in Seattle (Table 2).

Eligibility criteria common to all trials included: women aged 40–62 years; in the menopause transition (amenorrhea 60 days or more in the past year), or postmenopausal (12 months or more since last menstrual period or bilateral oophorectomy), or had a hysterectomy with one or both ovaries remaining and follicle-stimulating hormone greater than 20 mIU/mL and 50 pgm/mL E2 or less; and in general good health as determined by medical history, a brief physical examination, and standard blood tests. In addition to the screening vasomotor symptom frequency requirement (Table 1), for MsFLASH 01–03 trials vasomotor symptoms had to be rated as bothersome or severe on at least 4 days or night per week, and the frequency in screening week 3 could not decrease greater than 50% from the mean weekly levels in screening weeks 1 and 2.

Exclusion criteria common to all trials included: use of prescription or over-the-counter treatments for hot flushes (past 30 days); and use of exogenous sex steroid hormones or hormonal contraceptives (past 2 months).

Outcomes measures and follow-up

The outcome of interest for this joint analysis was menopause-related quality of life measured using the Menopause-Specific Quality of Life (MENQOL) questionnaire.[16] Participants completed the MENQOL at baseline, week 4, and week 8 in MsFLASH 01 and 03; at baseline and week 8 in MsFLASH 04; at baseline and week 12 of treatment in MsFLASH 02. This 29-item, validated questionnaire (range 1–8) assesses four quality of life domains; physical (16 items), vasomotor (3 items), psychosocial (7 items) and sexual (3 items). Scoring generates 4 domain scores and a total score, the mean of the 4 domain scores. Although no minimal clinically important difference for the MENQOL or its subscales has been established, a range has been suggested from 0.5 to 1.0.[17] The vasomotor domain assesses hot flushes, night sweats, and sweating. The psychosocial domain evaluates the psychological wellbeing of the individual by including items regarding anxiousness, memory, and feeling “blue.” The physical domain assesses symptoms such as flatulence,

bloating, pain, tiredness, sleeping, energy and weight gain. The sexual domain inquires about changes in sexual desire, vaginal dryness, and intimacy. Identical scoring for each of the four MENQOL domains is used. For each of the 29 items, the seven-point Likert scale is converted to an eight-point scale, ranging from 1 to 8. A “one” is equivalent to a woman responding “no”, indicating she had not experienced this symptom in the past month. A “two” indicated that the woman experienced the symptom, but it was not at all bothersome. Scores “three” through “eight” indicated increased levels of bother experienced from the symptom, and correspond to the “1” though “6” check boxes on the MENQOL. Once each item had been expressed as a 1–8 score, each domain was scored by averaging the values. Hence, the average for each domain was constrained between 1 (not at all a problem; respondent selected “no” for each item in the domain) to 8 (respondent reported experiencing each symptom in the domain at the highest degree of bother).[18]

Insomnia symptoms were measured using the Insomnia Severity Index (ISI), a valid and reliable self-administered instrument that measures perception of current (past 2 weeks) insomnia symptoms.[19,20] ISI scores theoretically range from 0–28, with higher scores indicating more severe insomnia symptoms. Sexual symptoms were assessed with the Female Sexual Function Index (FSFI) with scores ranging from 2–36[18] and the Female Sexual Distress Scale–Revised (FSDS) Item 1, with scores from 0–4.[21]

Statistical analysis

The intent-to-treat analysis included all randomized participants who provided follow-up MENQOL data, regardless of adherence to treatment assignment. Baseline demographic and clinical characteristics of participants as shown in Table 2 were compared across the 4 trials with homogeneity assessed using chi-square or F-test.

Linear regression models were applied to estimate differences in changes from baseline in MENQOL at weeks 4, 8, and 12 between each intervention group and its corresponding control group, with adjustment for trial number, clinical site, age, race, education level, smoking, and BMI. The models incorporated trial-specific effects of the baseline outcome measure and study time to allow the relationships between the baseline and follow-up MENQOL, and MENQOL with study time, to vary across trials. Thus, the models estimate each intervention effect relative to its own trial’s control group, while adjusting for common factors across trials. Robust standard errors were calculated by generalized estimating equations.

The planned sample size of each trial was determined by the primary trial endpoints. Analyses were conducted using SAS Version 9.3 (SAS Institute, Inc., Cary, NC).

RESULTS

A total of 1005 participants were randomized in the four trials: 104 to escitalopram and 101 to placebo (MsFLASH 01); 106 to exercise, 107 to yoga, and 142 to usual activity, and simultaneously, 177 to omega-3 and 178 to placebo (MsFLASH 02); 97 to estradiol, 96 to venlafaxine, and 146 to placebo (MsFLASH 03); 53 to CBT-I and 53 to menopause education (MsFLASH 04).

Follow-up data collection retention was high in all trials: 196 (96%) of 205 women randomized provided week 4 and/or week 8 MENQOL data in 01; 336 (95%) of 355 women provided MENQOL data at week 12 in 02; 328 (97%) of 339 randomized provided follow-up MENQOL data at week 4 and/or week 8 in 03; 81 (76%) of 106 randomized provided follow-up MENQOL data at week 8 in 04.

Age was similar across trials with an overall mean of 55 years (SD 4; range 42 to 65).The distributions of race, education levels, and smoking prevalence varied across studies, corresponding to the clinical site locations and goals of the trials. Although more than 35% of the women in MsFLASH 01–03 were non-white, in MsFLASH 04 over 90% were white, reflecting the fact that this trial was conducted only in one site (Seattle). Mean body mass index was lower in MsFLASH 04 compared to the other trials. The distribution of menopausal status was similar across trials. Mean baseline vasomotor symptom frequency was more than 7/day in all four trials, although mean baseline vasomotor symptom frequency and bother were higher in MsFLASH 01 than in the later trials due to more stringent vasomotor symptom eligibility criteria (Table 1). The mean ISI was higher in MsFLASH 04, reflecting the entry criteria for that trial (Table 1). Mean FSDS Item 1 was similar across the four trials; mean FSFI was lower in MsFLASH01, although the average FSFI in all trials was less than 20, suggesting that sexual dysfunction was common among participants (Table 1).[22]

Mean baseline total MENQOL scores were similar across trials (Table 2) (range 3.6–3.8). Mean baseline MENQOL vasomotor and psychological subscales differed among the 4 trials, reflecting the differences in symptom eligibility criteria among the trials. MsFLASH 01, which required more VMS symptoms, had a higher mean MENQOL vasomotor subscale score, while MsFLASH 04, which required bothersome insomnia symptoms, had a higher mean MENQOL psychosocial subscale score at baseline.

Mean relative reductions from baseline in the control groups ranged from 0.5–0.7 for total MENQOL, from 0.8–1.3 for MENQOL vasomotor subscale, from 0.3–0.6 for MENQOL psychosocial subscale, from 0.4–0.7 MENQOL physical subscale, and from 0.2–0.7 for MENQOL sexual subscale. (Table 3)

Reductions in total MENQOL scores from baseline of similar size across trials and significamt reductions were observed in the estradiol, escitalopram, and CBT-I groups relative to control at week 8 (Table 4; Figure 1). Decreases in total MENQOL ranged from 0.4 to 0.5 lower with each of these interventions, relative to control (Table 4). A more modest but significant reduction in total MENQOL of 0.3 was observed in the yoga group at week 12, relative to control.

The largest improvement in the vasomotor subscale was observed in the estradiol group, and more modest effects were seen in the escitalopram, yoga and CBT-I groups” (Table 4, Figure 2). Substantial improvements in the psychosocial subscale of the MENQOL from baseline were observed for the escitalopram and venlafaxine groups (Table 4, Figure 3). For the physical subscale of the MENQOL, the greatest improvement relative to control was observed for CBT-I and exercise. (Table 4, Figure 4). For the sexual subscale, the greatest

improvement was observed for CBT-I, with yoga and estradiol showing smaller effects relative to control (Table 4, Figure 5).

In sensitivity analyses, we limited the analysis to participants with an ISI ≥12, consistent with inclusion criteria for MsFLASH 04, which was focused on insomnia symptoms as the primary outcome. Ninety-three women met this criterion in MsFLASH 01, 173 women in MsFLASH02, 150 women in MsFLASH 03, and all 81 women in MsFLASH 04 (total 497). In this analysis, results were similar to the primary analysis.

No serious adverse events due to study interventions were reported during the four trials.[5–7,9–11] All study medications were well-tolerated and no participants stopped the exercise, yoga, or CBT-I interventions due to side effects.

DISCUSSION

In this analysis of pooled individual-level data from four MsFLASH clinical trials, a modest improvement in overall menopause-related quality of life was observed for estradiol, escitalopram, CBT-I, and yoga groups relative to control in women with bothersome vasomotor symptoms (Table 4; Figure 4).

For the vasomotor subscale, the largest improvement was observed in the estradiol group, although improvements were of similar size and significance for the escitalopram, CBT-I, and yoga groups relative to control. (Table 4, Figure 2). The largest improvements in the psychosocial subscale of the MENQOL from baseline were observed for CBT-I, escitalopram, and venlafaxine. For the sexual and physical subscales, the greatest improvement relative to control was observed for CBT-I, although the confidence intervals for these estimates were wide.

These results are consistent with other trials of these interventions that evaluated their effect on menopause-related quality of life. Low dose estrogen[23], SSRIs[23,24], and yoga[25] have been associated with improvements in menopause-related quality of life in other studies. Our finding that exercise improved MENQOL physical function compared to control but was not associated with overall menopause-related QOL is also consistent with other work.[26,27] CBT-I effects on menopause-related QOL has not been studied in other trials, nor are we not aware of other work examining the effects omega-3-fatty acid supplementation on menopause-related quality of life.

The magnitude of the benefit seen with many of the interventions was generally small, in the range of a 0.5 difference in change in the total MENQOL and subscales. Although no minimal clinically important difference for the MENQOL or its subscales has been established, a range has been suggested from 0.5 to 1.0.[17] Women in the intervention groups with favorable changes in the MENQOL did report overall higher treatment satisfaction compared to controls, suggesting these differences were clinically significant.[6,7,11]

These results suggest that with respect to menopause-related quality of life, women have a variety of treatment strategies to choose from and can select an approach based on their most bothersome symptoms and their individual preferences. For women for whom VMS are the

most bothersome quality of life concern, estradiol is the most efficacious treatment, but other nonhormone pharmacologic and non-pharmacologic options are also beneficial. For women for whom psychosocial symptoms are most bothersome, these results suggest that escitalopram, venlafaxine, or CBT-I are reasonable approaches to consider. For women with insomnia and bothersome vasomotor symptoms, the observed effect of CBT-I on menopause-related quality of life overall and on subscales of the MENQOL that might not obviously be related to sleep (for e.g., the sexual subscale) highlights the importance of sleep in overall quality of life and optimal functioning in a variety of domains.

Effects of CBT-I on women's ratings of bother associated with several symptom groups (total MENQOL score and vasomotor, physical, and sexual subscale scores) is consistent with McCurry's finding that CBTI not only was associated with an improvement in sleep symptoms, but also improvement in interference associated with vasomotor symptoms. (CIT).[11] The current results prompt us to consider the effects of CBT on a range of symptoms and the mechanisms by which the CBT-I intervention affected ratings of health-related quality of life beyond improving sleep. The intervention tested in that trial included elements of sleep restriction, stimulus control, sleep hygiene education, cognitive restructuring with behavioral homework as well as menopause education, e.g. information about the menopausal transition. Although some dimensions of CBT-I were specific to sleep, the more general strategies for managing symptoms and distress or bother related to symptoms may affect a wide range of symptoms. Other work hasfound that group and self-help CBT interventions including psychoeducation, stress management, paced breathing/ relaxation, and cognitive and behavioral strategies for managing symptoms including individual goal setting and homework, are effective in helping women manage problematic hot flashes and night sweats experienced in conjunction with breast cancer as well as in occupational settings.[28–30] Thus CBT-I as well as CBT for menopause-related symptoms incorporate multiple therapeutic dimensions that may support women's capacity to manage their symptoms more effectively, thus relieving symptom-related bother and interference with daily life.

Strengths of this pooled analysis include the use of standardized methods for measurement of participant characteristics, menopause-related quality of life, VMS, other menopausal symptoms, and similar inclusion and exclusion criteria. The MsFLASH trials were designed to be comparable, though not identical, making this multivariable analysis an important step in comparing estimates of the seven intervention effects on selected outcomes. A single trial designed to provide direct head-to-head comparisons of all interventions would not be feasible. We could not evaluate combinations of treatments, but it might be useful to women to try combinations to improve QOL; for example, a non-pharmacologic treatment such as yoga or CBT-I might be combined with a pharmacologic treatment or two non-pharmacologic treatments, such as CBT-I and yoga may be benefit when insomnia symptoms are present.

CONCLUSIONS

Vasomotor and other symptoms associated with menopause cause significant distress for many women and negatively impact their health related quality of life. While estrogen

supplementation has been the most widely recommended therapy, results from this pooled analysis demonstrate that a variety of treatment approaches provide improvement in HRQOL among menopausal women with vasomotor symptoms; using this information women can select an approach based on most bothersome symptoms and individual preferences.

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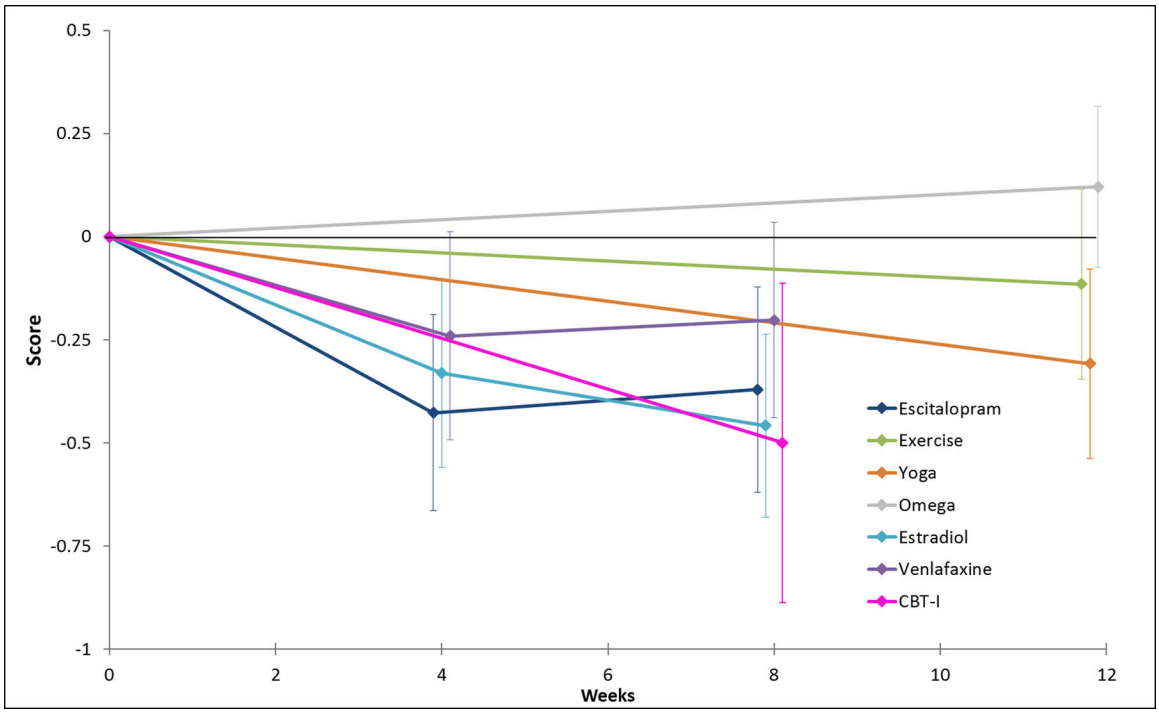

Figure 1.
Effect of each intervention relative to control on changes from baseline in MENQOL Total score

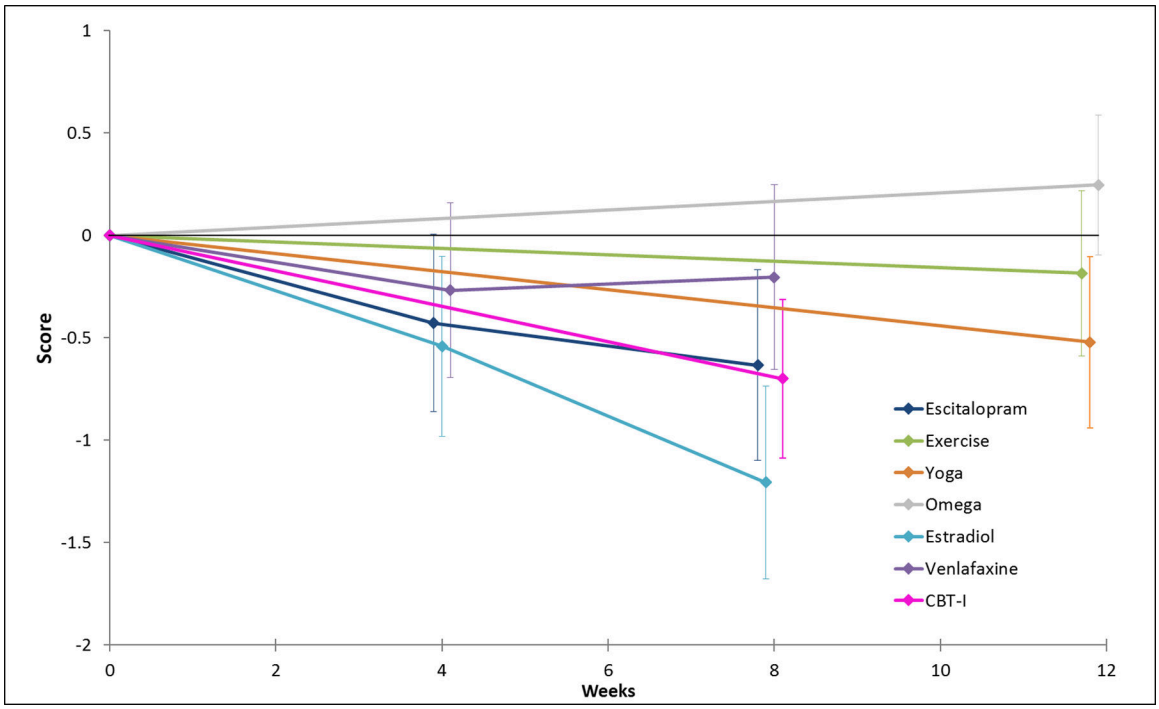

Figure 2.

Effect of each intervention relative to control on changes from baseline in MENQOL Vasomotor domain score

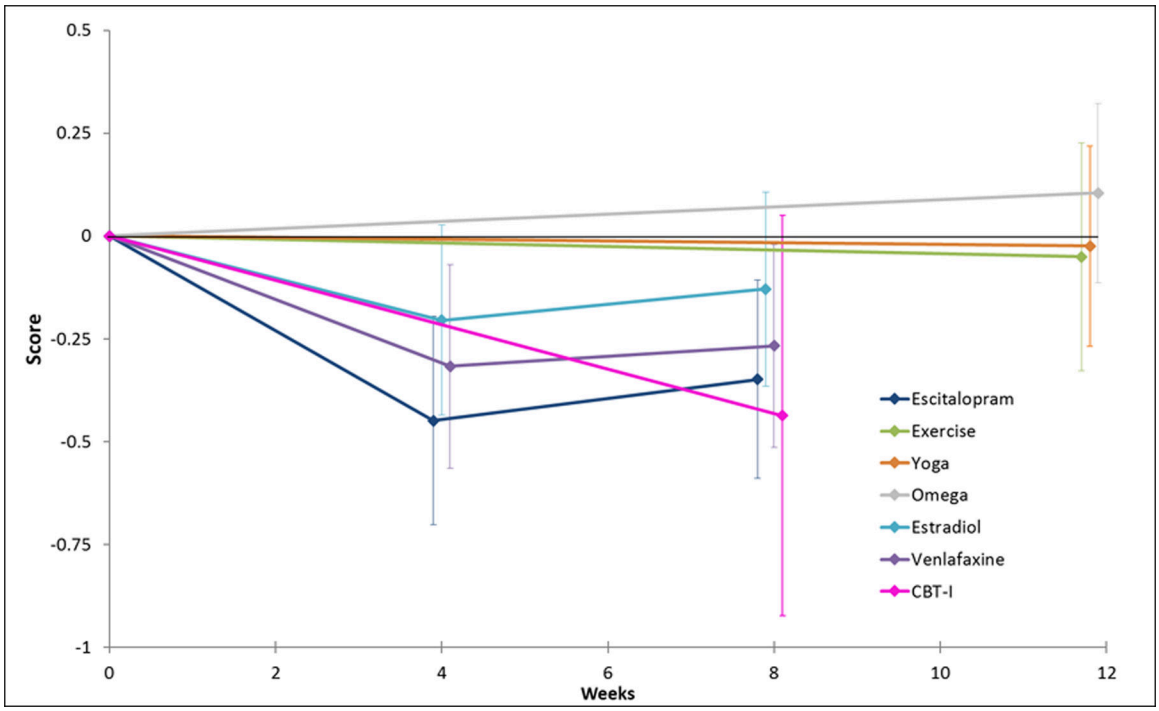

Figure 3.

Effect of each intervention relative to control on changes from baseline in MENQOL Psychosocial domain score

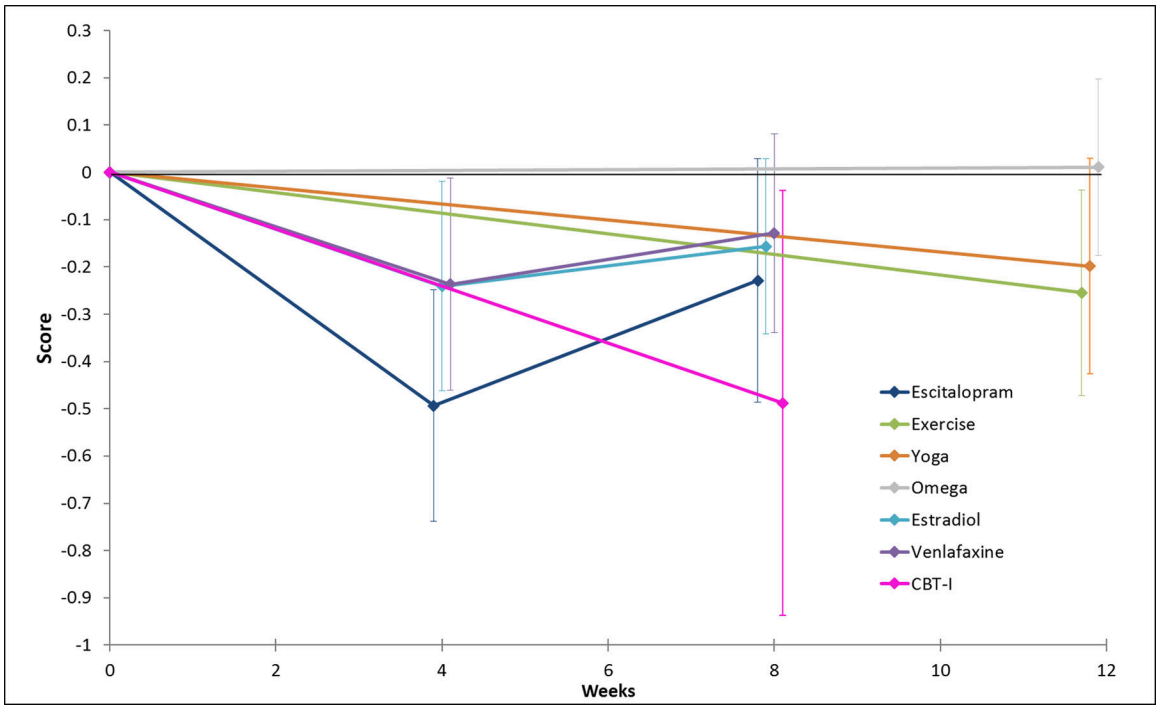

Figure 4.

Effect of each intervention relative to control on changes from baseline in MENQOL Physical domain score

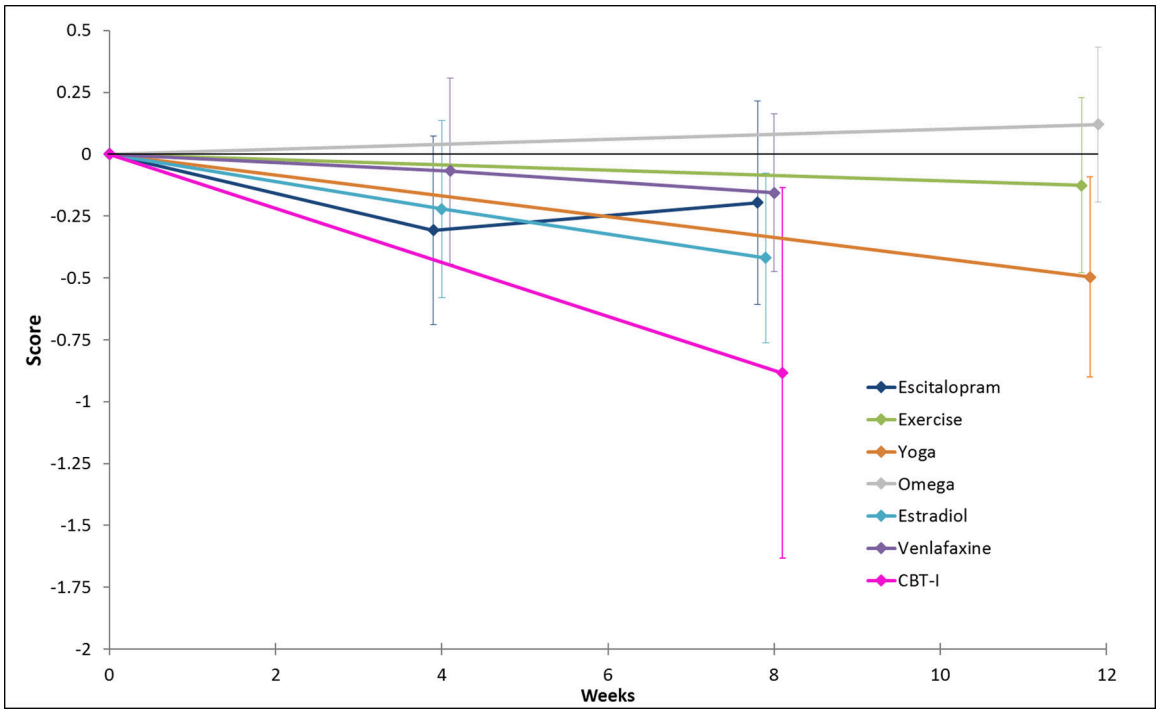

Figure 5.
Effect of each intervention relative to control on changes from baseline in MENQOL Sexual domain score

Table 1.

Summary of MsFLASH Trials

Trial	Total enrollment	Design	Hot flash + insomnia eligibility	Trial-specific exclusion criteria	Intervention length	MENQOL assessment
01	205; 196 eligible for this analysis	2-arm: Escitalopram vs. placebo	≥28 hot flashes/ week	• Use of psychotropic medications (past 30 days) • Use of gabapentin, pregabalin, triptans, warfarin, or St. John's Wort • Use of selective estrogen receptor modulators or aromatase inhibitors (past 60 days) • Suicide attempt in the past 3 years • History of endometrial or ovarian cancer	8 weeks	Baseline Week 4 Week 8
02	355; 336 eligible for this analysis	3 × 2 factorial: Aerobic exercise and yoga vs. usual activity, plus omega-3 supplementation vs. placebo	≥14 hot flashes/ week	• Body mass index >37 kg/m^2 • Contraindications to yoga, exercise training, or omega-3 • Current participation in yoga or regular exercise • Current use of omega-3 supplements • Consumption ≥4 servings of fish/week	12 weeks	Baseline Week 12
03	339; 328 eligible for this analysis	3-arm: Low dose oral estradiol and venlafaxine vs. placebo	≥14 hot flashes/ week	• Hypersensitivity or contraindication to study medications • Use of psychotropic medications (past 30 days) • Use of selective estrogen receptor modulators or aromatase inhibitors (past 60 days) • Suicide attempt in the past 3 years • History of thrombotic or endometrial disease, pre-breast cancer conditions, or breast cancer	8 weeks	Baseline Week 4 Week 8
04	106; 81 eligible for this analysis	2-arm: Telephone cognitive behavior therapy for insomnia vs. menopause education control	≥14 hot flashes/ week Insomnia Severity Index ≥12 (at both screening and baseline)	• Known primary sleep disorder diagnosis • Works job with rotating shifts >3 times per week • Routine use of prescription sleeping or sedating medication at night (>3 times per week)	8 weeks	Baseline Week 8

Abbreviations: MENQOL, Menopause-related Quality of Life

Table 2.

Baseline demographic and clinical characteristics by trial among participants with MENQOL data for at least one domain both at baseline and follow-up

Baseline Characteristic	MsFLASH 01	MsFLASH 02	MsFLASH 03	MsFLASH 04	p-value
Age at Screening, mean (SD)	53.9 (4.1)	54.8 (3.7)	54.6 (3.8)	55.6 (3.9)	0.006
<50	23 (11.7)	19 (5.7)	28 (8.5)	2 (2.5)	
50–54	91 (46.4)	148 (44.0)	142 (43.3)	33 (40.7)	
55–59	62 (31.6)	127 (37.8)	120 (36.6)	32 (39.5)	
≥60	20 (10.2)	42 (12.5)	38 (11.6)	14 (17.3)	
Race, n (%)					<0.001
African American	87 (44.4)	90 (26.8)	106 (32.3)	1 (1.2)	
White	101 (51.5)	215 (64.0)	202 (61.6)	76 (93.8)	
Other	8 (4.1)	31 (9.2)	20 (6.1)	4 (4.9)	
Hispanic	0 (0.0)	5 (1.5)	1 (0.3)	2 (2.5)	
American Indian	1 (0.5)	6 (1.8)	2 (0.6)	1 (1.2)	
Asian / Pacific Islander	3 (1.5)	12 (3.6)	5 (1.5)	0 (0.0)	
Undisclosed	4 (2.0)	8 (2.4)	12 (3.7)	1 (1.2)	
Education, n (%)					<0.001
≤ High school diploma / GED	36 (18.4)	19 (5.7)	52 (15.9)	4 (4.9)	
Post-high school	83 (42.3)	103 (30.7)	108 (32.9)	15 (18.5)	
College graduate	77 (39.3)	213 (63.4)	168 (51.2)	62 (76.5)	
Married / Marriage-like Relationship, n (%)					0.02
No	80 (40.8)	111 (33.0)	121 (36.9)	16 (19.8)	
Yes	116 (59.2)	223 (66.4)	207 (63.1)	65 (80.2)	
Smoking, n (%)					<0.001
Never	96 (49.0)	221 (65.8)	170 (51.8)	63 (77.8)	
Past	58 (29.6)	84 (25.0)	106 (32.3)	18 (22.2)	
Current	42 (21.4)	29 (8.6)	50 (15.2)	0 (0.0)	
Body Mass Index, m/kg^2, mean (SD)	29.1 (6.6)	27.0 (4.4)	28.2 (6.7)	24.9 (5.0)	<0.001
< 25	52 (26.5)	115 (34.2)	116 (35.4)	50 (61.7)	
25 - <30	68 (34.7)	136 (40.5)	103 (31.4)	16 (19.8)	
≥ 30	75 (38.3)	85 (25.3)	102 (31.1)	15 (18.5)	

Baseline Characteristic	MsFLASH 01	MsFLASH 02	MsFLASH 03	MsFLASH 04	p-value
Menopause status, n (%)					0.28
Postmenopausal	136 (69.4)	254 (75.6)	248 (75.6)	54 (66.7)	
Perimenopausal	41 (20.9)	61 (18.2)	51 (15.5)	23 (28.4)	
Indeterminate	19 (9.7)	21 (6.3)	29 (8.8)	4 (4.9)	
Site, n (%)					
Boston	40 (20.4)	0 (0.0)	99 (30.2)	0 (0.0)	
Indianapolis	32 (16.3)	108 (32.1)	0 (0.0)	0 (0.0)	
Oakland	55 (28.1)	108 (32.1)	0 (0.0)	0 (0.0)	
Philadelphia	69 (35.2)	0 (0.0)	111 (33.8)	0 (0.0)	
Seattle	0 (0.0)	120 (35.7)	118 (36.0)	81 (100.0)	
MENQOL Total, mean (SD)	3.8 (1.3)	3.8 (1.1)	3.6 (1.1)	3.8 (1.1)	0.08
MENQOL Vasomotor, mean (SD)	5.9 (1.7)	5.4 (1.5)	5.7 (1.6)	5.2 (1.6)	<0.001
MENQOL Psychosocial, mean (SD)	2.9 (1.5)	3.2 (1.5)	2.8 (1.5)	3.4 (1.4)	<0.001
MENQOL Physical, mean (SD)	3.2 (1.3)	3.2 (1.3)	3.1 (1.3)	3.5 (1.2)	0.04
MENQOL Sexual, mean (SD)	3.3 (2.5)	3.3 (2.3)	2.9 (2.2)	2.3 (0.3)	0.24
Hot flash frequency, mean (SD)	9.8 (5.7)	7.6 (3.9)	8.0 (5.1)	7.7 (4.5)	<0.001
Hot flash severity, mean (SD)	2.2 (0.4)	2.0 (0.4)	2.0 (0.5)	1.7 (0.4)	<0.001
ISI, mean (SD)	11.3 (6.3)	11.7 (5.4)	10.9 (6.0)	15.9 (3.5)	<0.001
FSFI, mean (SD)	16.2 (11.9)	18.4 (10.5)	19.4 (10.5)	19.3 (10.6)	0.01
FSDS, mean (SD)	1.5 (1.3)	1.6 (1.2)	1.5 (1.2)	1.8 (1.3)	0.27

Abbreviations: MENQOL, Menopause-related Quality of Life; ISI, Insomnia Severity Index; FSFI, Female Sexual Function Index; FSDS, Female Sexual Distress Scale–Revised

Ranges: MENQOL Total 1–8; MENQOL Vasomotor 1–8; MENQOL Psychosocial 1–8; MENQOL Physical 1–8; MENQOL Sexual 1–8; ISI 0–28; FSFI 2–36; FSDS 0–4;

Table 3.

Changes from baseline in daily mean MENQOL in MsFLASH trial control groups

	Mean (95% CI)		
Outcome	**Week 4 – Baseline**	**Week 8 – Baseline**	**Week 12 – Baseline**
MENQOL Total			
Trial 1	−0.5 (−0.7, −0.3)	−0.7 (−0.9, −0.5)	--
Trial 2	--	--	−0.7 (−0.9, −0.5)
Trial 3	−0.6 (−0.7, −0.4)	−0.7 (−0.9, −0.5)	--
Trial 4	--	−0.6 (−0.9, −0.5)	--
MENQOL Vasomotor			
Trial 1	−1.0 (−1.3, −0.7)	−1.0 (−1.4, −0.6)	--
Trial 2	--	--	−1.3 (−1.8, −0.9)
Trial 3	−0.8 (−1.1, −0.6)	−1.1 (−1.4, −0.8)	--
Trial 4	--	−0.8 (−1.4, −0.2)	--
MENQOL Psychosocial			
Trial 1	−0.3 (−0.5, −0.1)	−0.6 (−0.8, −0.4)	--
Trial 2	--	--	−0.5 (−0.8, −0.3)
Trial 3	−0.3 (−0.5, −0.2)	−0.4 (−0.6, −0.3)	--
Trial 4	--	−0.5 (−0.9, −0.0)	--
MENQOL Physical			
Trial 1	−0.5 (−0.7, −0.3)	−0.7 (−0.9, −0.5)	--
Trial 2	--	--	−0.4 (−0.6, −0.2)
Trial 3	−0.5 (−0.6, −0.3)	−0.6 (−0.8, −0.5)	--
Trial 4	--	−0.4 (−0.7, −0.1)	--
MENQOL Sexual			
Trial 1	−0.5 (−0.8, −0.1)	−0.7 (−1.1, −0.4)	--
Trial 2	--	--	−0.4 (−0.9, 0.0)
Trial 3	−0.5 (−0.8, −0.2)	−0.6 (−0.9, −0.4)	--
Trial 4	--	−0.2 (−0.7, 0.3)	--

Abbreviations: MENQOL, Menopause-related Quality of Life

Ranges: MENQOL Total 1–8; MENQOL Vasomotor 1–8; MENQOL Psychosocial 1–8; MENQOL Physical 1–8; MENQOL Sexual 1–8;

Table 4.

Effect of each intervention relative to control on changes from baseline in MENQOL

Outcome	Intervention	Week 4 - baseline Mean (95% CI)	Week 8 - baseline Mean (95% CI)	Week 12 - baseline Mean (95% CI)
MENQOL Total				
Trial 01	Escitalopram	−0.4 (−0.7, −0.2)	−0.4 (−0.6, −0.1)	--
Trial 02	Exercise	--	--	−0.1 (−0.3, 0.1)
	Yoga	--	--	−0.3 (−0.5, −0.1)
	Omega-3	--	--	0.1 (−0.1, 0.3)
Trial 03	Estradiol	−0.3 (−0.6, −0.1)	−0.5 (−0.7, −0.2)[a]	--
	Venlafaxine	−0.2 (−0.5, 0.0)	−0.2 (−0.4, 0.0)	--
Trial 04	CBT-I	--	−0.5 (−0.9, −0.1)[a]	--
MENQOL Vasomotor				
Trial 01	Escitalopram	−0.4 (−0.9, 0.0)	−0.6 (−1.1, −0.2)[a]	--
Trial 02	Exercise	--	--	−0.2 (−0.6, 0.2)
	Yoga	--	--	−0.5 (−0.9, −0.1)[a]
	Omega-3	--	--	0.2 (−0.1, 0.6)
Trial 03	Estradiol	−0.5 (−1.0, −0.1)[a]	−1.2 (−1.7, −0.7)[a]	--
	Venlafaxine	−0.3 (−0.7, 0.2)	−0.2 (−0.7, 0.2)	--
Trial 04	CBT-I	--	−0.7 (−1.3, −0.1)[a]	--
MENQOL Psychosocial				
Trial 01	Escitalopram	−0.4 (−0.7, −0.2)	−0.3 (−0.6, −0.1)	--
Trial 02	Exercise	--	--	−0.1 (−0.3, 0.2)
	Yoga	--	--	0.0 (−0.3, 0.2)
	Omega-3	--	--	0.1 (−0.1, 0.3)
Trial 03	Estradiol	−0.2 (−0.4, 0.0)	−0.1 (−0.4, 0.1)	--
	Venlafaxine	−0.3 (−0.6, −0.1)	−0.3 (−0.5, 0.0)	--
Trial 04	CBT-I	--	−0.4 (−0.9, 0.1)	--
MENQOL Physical				

Outcome	Intervention	Week 4 - baseline Mean (95% CI)	Week 8 - baseline Mean (95% CI)	Week 12 - baseline Mean (95% CI)
Trial 01	Escitalopram	−0.5 (−0.7, −0.2)[a]	−0.2 (−0.5, 0.0)	--
Trial 02	Exercise	--	--	−0.3 (−0.5, 0.0)
	Yoga	--	--	−0.2 (−0.4, 0.0)
	Omega-3	--	--	0.0 (−0.2, 0.2)
Trial 03	Estradiol	−0.2 (−0.5, 0.0)	−0.2 (−0.3, 0.0)	--
	Venlafaxine	−0.2 (−0.5, 0.0)	−0.1 (−0.3, 0.1)	--
Trial 04	CBT-I	--	−0.5 (−0.9, 0.0)[a]	--
MENQOL Sexual				
Trial 01	Escitalopram	−0.3 (−0.7, 0.1)	−0.2 (−0.6, 0.2)	--
Trial 02	Exercise	--	--	−0.1 (−0.5, 0.2)
	Yoga	--	--	−0.5 (−0.9, −0.1)[a]
	Omega-3	--	--	0.1 (−0.2, 0.4)
Trial 03	Estradiol	−0.2 (−0.6, 0.1)	−0.4 (−0.8, −0.1)	--
	Venlafaxine	−0.1 (−0.4, 0.3)	−0.2 (−0.5, 0.2)	--
Trial 04	CBT-I	--	−0.9 (−1.6, −0.1)[a]	--

Abbreviations: MENQOL, Menopause-related Quality of Life; CBT-I, cognitive behavioral therapy for insomnia

Ranges: MENQOL Total 1–8; MENQOL Vasomotor 1–8; MENQOL Psychosocial 1–8; MENQOL Physical 1–8; MENQOL Sexual 1–8.

[a]Notes interventions that had at least a 0.5 change from baseline in the score