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An Open Label Pilot Study to Evaluate The Effectiveness of A Proprietary Krill Oil Formulation in the Relief of Troublesome Symptoms of the Menopause

Pharma

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ABSTRACT

The effectiveness of a proprietary formulation in relieving the most troublesome symptoms of the menopause was assessed in an open label pilot study over 4 months. The supplement providing thiamine, riboflavin, pyridoxine, vitamin D, soy isoflavones, rosemary extract and krill oil was taken each day for the 3 months of the active phase of the trial. After the first month of treatment, compared to baseline, highly statistically significant effects were reported by 50 women who completed the study regarding hot flush intensity; hot flush frequency; difficulty sleeping; mood symptoms; feeling down; lack of drive; verge of tears; mood swings; anxiety; irritation; lack of sex drive; dryness of the vagina and increased need to urinate. These improvements increased in a highly statistically significant manner during the next 30 days and remained at this elevated level through to the trial end. A further larger placebo controlled trial is proposed.

Background

Given the enhanced longevity now enjoyed in many societies, such as US, many more women spend more than a third of their life post-menopausal and this is expected to continue to rise (1,2). The average age of menopause in the UK is 51 (3).

Around 80% of women experience some symptoms during the menopause, typically lasting about 4 years after the last period, but continuing for up to 12 years in about 10% of women (4). Those menopausal symptoms that have been shown to be associated with the onset of the menopausal transition are vasomotor symptoms (hot flushes and night sweats), vulvovaginal atrophy/dyspareunia, sleep disturbance, and adverse mood, a lack of interest in sex, headaches, and joint and muscle stiffness, memory and concentration loss, and consequently quality of life may be severely affected (5-8).

The clinical rationale for the supplement formula

Given the issues with the potential safety and side effects of many prescribed medications, the lack of efficacy of a number of lifestyle interventions and the clear desire from many women to initially use more natural approaches, there is a need to identify an effective nutritional solution as a first line strategy in the management of menopausal symptoms.

Krill oil as a source of Omega 3 fatty acids

There are a number of clinical trials suggesting supplementation with Omega 3 fatty acids in relations to depression, anxiety, and enhancing mood (9-13).

The formulation under evaluation has previously been the subject of an open label study in PMS, and reported to be highly statistically significantly effective in terms of relieving symptoms similarly common in menopause such as anxiety, fatigue, forgetfulness, insomnia and headache (14).

B vitamins

Vitamins B1,B2,B3 and B6 are required for generating those neurotransmitters that might impact upon the pathophysiology of menopause. Vitamin B6 in especially important since it is involved in the balance of adequate glutathione/glutathione disulphide (GSH/GSSG) levels which is relevant to women of menopausal or postmenopausal age (15-18).

Soy Isoflavones

A recent Cochrane review of natural phytoestrogen sources such as soya and red clover found some trials reported a slight reduction in hot flushes and night sweats with phytoestrogen-based treatment (19).

Rosemary extract

Rosemary has traditionally been used for its anti-depressive effect and new data suggests this could be due to modulation of the cholinergic and monoaminergic systems (20).

Vitamin D3

Vitamin D and its analogs have been widely employed in the prevention and treatment of post-menopausal osteoporosis. New research demonstrates that Vitamin D also plays a role in the regulation of vaginal stratified squamous epithelial cell growth and differentiation therefore may be of benefit in this respect (21).

Astaxanthin

Astaxanthin, a xanthophyll carotenoid, is naturally present in krill oil and is a powerful, broad-ranging antioxidant (22).

Methods and materials

Recruitment and screening

Recruitment of potential participants was undertaken by Talk Health an organisation with a large database of individuals who have self-identified as suffering from a wide range of conditions, including menopausal symptoms.

Inclusion criteria:- women aged between 45 and 59 years old; presenting with a subjective complaint of problematic menopausal symptoms for a minimum of three days per week for a period of at least 3 months.

Exclusion criteria:-Evidence that menopausal symptoms are directly related to a severe or unstable medical disorder or severe psychiatric disorder (e.g.,bipolar disorder, schizophrenia); presence of sleep apnea or periodic limb movements during sleep; presence of major depression or other severe psychopathology; Patients receiving HRT, clonidine, SSRI medications (antidepressants), Isoflavone containing supplements, Omega 3 or 6 supplements

Symptom severity was assessed using a Menopause Rating Scale (MRS) which measures menopausal or climacteric symptoms in a standardized way (23,24) and was validated some years ago (25-27). It aims to establish an instrument that measures health related quality of life that can easily be completed. The original German scale has been translated into English and culturally adapted (28).

Following recruitment, each participant was asked to complete the MRS questionnaire over each month of the study, and rank the typical impact of menopausal symptoms they were experiencing through from baseline to completion.

These problems included - Hot flushes intensity; Hot flush frequency; Difficulty sleeping; Mood symptoms; Feeling Down; Lack Of Drive; Verge of tears; Mood swings; Anxiety; Irritation; Lack of sex drive; Dryness of the vagina; Increased need to urinate.

Following the one month baseline assessment each patient took two capsules each day with meals for the three months, and were instructed not to make significant changes to their usual diet. Each patient then completed the MRS questionnaires during each of the following 3 three months.

Each dose of the krill oil compound supplement contains thiamine hydrochloride 1.4mg, riboflavin 1.6mg, pyridoxine hydrochloride 2mg, standardised soy isoflavones 50mg-(S101), standardised rosemary extract (S102) 50mg in soft gelatin capsules containing 350mg of krill oil. 2 capsules were taken each day during the active phase of the trial.

Results

There was a highly statistically significant improvement in all of the symptoms assessed at the end of the first month of supplementation compared to the baseline assessments from between 15% to 34% and these continued to increase at the end of the second month to between 22% and 39%. This improvement was general maintained to the same extent at the end of the 120 day assessment. Since there was no statistically significant change from day 60 and day 90 scores, only day 60 and day 90 results are included in the summary table (I) below

Table I-Summary of changes in menopausal symptom scores recorded by patients at day 30 and day 60 compared to baseline following consumption of Clean Marine Krill Oil for Women

symptom (n=50)	baseline mean score (SD)	60 day mean score (SD)	difference in mean (95%CL)	p value	% improvement	90 day mean score (SD)	difference in mean (95%CL)	p value	% improvement
Intensity of hot flushes	3.22(1.13)	2.56 (0.93)	0.66(0.39 to 0.93)	<0.0001	21%	2.36 (0.88)	0.86(0.56 to 1.16)	p<0.001	27%
frequency of hot flushes	3.4(1.01)	2.88 (0.94)	0.52(0.18 to 0.86)	<0.003	15%	2.66 (0.85)	0.74(0.42 to 1.06)	<0.0001	22%
sleep	3.44 (0.99)	2.76 (1.19)	0.68 (0.34-1.02)	<0.0002	20%	2.40 (0.9)	1.04 (0.74 to 1.32)	<0.0001	30%
mood	3.30 (0.96)	2.66 (0.82)	0.64 (0.35 to 0.93)	<0.0001	19%	2.38 (0.88)	0.92 (0.66 to 1.18)	<0.0001	28%
feeling down	3.10 (1.2)	2.46 (1.01)	0.64 (0.36 to 0.92)	<0.0001	21%	2.20 (0.99)	0.90 (0.61 to 1.19)	<0.0001	29%
lack of drive	3.12 (1.19)	2.40 (1.14)	0.72 (0.37 to 1.07)	<0.002	23%	2.06 (0.96)	1.06 (0.69 to 1.43)	<0.0001	34%
verge of tears	2.86 (1.13)	2.18 (1.16)	0.68 (0.36 to 1.00)	<0.0001	24%	1.96 (0.83)	0.92 (0.60 to 1.24)	<0.0001	32%
mood swings	3.12 (1.10)	2.26 (0.94)	0.86 (0.45 to 1.27)	<0.0001	27%	1.98 (0.82)	1.14 (0.75 to 1.53)	<0.0001	37%
anxiety	2.86 (1.21)	2.10 (1.05)	0.76 (0.31 to 1.21)	<0.0012	26%	2.12 (0.90)	0.74 (0.32 to 1.16)	<0.0014	26%
lack of sex drive	2.9 (1.16)	2.12 (0.86)	0.78 (0.40 to 1.19)	<0.0001	27%	1.76 (0.81)	1.14 (0.76 to 1.49)	<0.0001	39%
vaginal dryness	2.56 (0.94)	1.68 (0.80)	0.88 (0.47 to 1.19)	<0.0001	34%	1.66 (0.81)	0.90 (0.63 to 1.17)	<0.0001	35%
increased need to urinate	2.66 (0.83)	1.96 (0.83)	0.70 (0.39 to 1.05)	<0.0001	26%	1.72 (0.80)	0.94 (0.66 to 1.19)	<0.0001	35%

No adverse reactions were reported and within the beneficial changes in symptom scores the following trends were noted

Hot Flushes
Intensity

The change in reports between day baseline and day 60 were significant. In that interval, the proportion of women reporting either severe or very severe symptoms declined from 44% to only 10%; meanwhile those women reporting either no symptoms or only mild symptoms rose from 26% to 44%.

Frequency

There was a substantial initial reduction between baseline and day 60: the portion of respondents experiencing flushes 'often' or 'always' decreased in that interval from 56% to 25%, while the portion experiencing flushes 'never' or 'little' increased from 18% to 34%.

Sleep-related Symptoms

Reports of no difficulty sleeping through the night rose throughout the test: from only 3% at day zero to 14% at day 60, 15% at day 90, and 20% at day 120.

Mood-related Symptoms

Only 5% of participants reported no such mood effects at the start of the test, while 43% reported experiencing such effects 'often' or 'always'. By the end of the test, these numbers had risen to 14% and fallen to 12% respectively. By the end of the study, 62% reported having their mood affected either 'never' or 'little' – up from only 16% at the start of the test.

Feeling down: At the start of the study, 34% of participants reported no symptoms or only mild symptoms in this area. By the end of the study, that number had risen to 64%.

Lack of drive: The proportion of women reporting a lack of drive fell sharply, from 53% to 33% between baseline and day 60 and again to 27% at day 90.

Verge of tears: The percentage of women reporting being on the verge of tears also fell between baseline and day 60 – from 32% to 13% - it remained roughly the same until test end.

Mood swings: The proportion reporting mood swings fell throughout: from 20% to 8%.

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Anxiety: Reports of no anxiety or only mild anxiety rose throughout: from 38% at baseline immediately up to 64% at day 60, 65% at day 90 and 71% at day 120.

Capabilities
The total portion of women reporting either no memory difficulties or only mild difficulties rose substantially: from 31% up to 54% at day 60 and then to 75%. At the other end of the scale, the portion reporting intense or very intense symptoms fell sharply from 36% to 12% between baseline and day 60, then only 4% at day 90.

Sex Life
In addition to the above, participants were asked specifically (at day zero) how far the menopause had affected their sexual desire, their sexual activity, and their sexual satisfaction. In each case, the proportion reporting either intense or very intense effects from their symptoms had fallen from around 36% at baseline to 10% or lower by day 90, while the portion reporting no such effects had more than doubled.

Vaginal Symptoms
The percentage of participants reporting intense or very intense sensations halved between day zero and day 30, and again between day 30 and day 60 – from 28% down to 14%, then down to 7%. The percentage reporting no such symptom climbed in the same interval from 33% to 58% and 65%.

Bladder-related Symptoms
Reports of increased need to urinate fell steadily throughout. The numbers of respondents reporting no such symptoms rose from 33% at day zero up to 37% at day 30 and 45% and at day 60. From start to end, the number of respondents reporting intense or very intense symptoms fell consistently from 26% to only 2%, with no participants at all reporting very intense symptoms by day 90.

Discussion
An estimated 1.2 billion women will be either menopausal or postmenopausal, either naturally or surgically, by the year 2030 (29).Menopause-related symptoms, such as hot flushes and night sweats, remain highly prevalent even 10 or more years after the commencement of menopause (30).

Hormone replacement therapy (HRT), which is the most widely used therapy in this field, has become subject to controversial discussions over the past years, beginning in 2002 with the publication of the Women's Health Initiative (WHI) study. Concerns about harms of HRT outweighing the benefits lead to reductions in use of HRT in the following years. Although it has to be questioned, if the WHI trial had statistical errors, the lay press primarily focused on the publication of negative effects, including in UK. The result was a decrease in prescription of hormonal therapies. Due to on-going climacteric symptoms, many women switched to CAM. The evidence-based efficacy of CAM is little observed in prospective clinical trials, which have diverse results (31). Nevertheless more than a third of women use CAM in the treatment of climacteric symptoms (32).

A study conducted in US indicated the significant positive associations between use of vitamins/supplements and vasomotor symptoms; between use of vitamins/supplements and somatic symptoms; and between use of herbal medicines and psychological symptoms amongst menopausal women younger than 50 years (33). Despite the popularity of self-prescribed CAM use by women with menopausal symptoms, a majority of them do experience difficulty in their decision-making around choosing specific forms of self-prescribed CAM for frequently reported menopause-related symptoms (34) and do not inform the healthcare providers about their CAM use (62).

There is limited prior data investigating the potential role of Omega 3 fatty acids to relieve typical symptoms of the menopause. However, this pilot study demonstrates that the provision of these essential dietary components in the form of krill oil, together with specific B vitamins, vitamin D and botanicals such as soy isoflavones and rosemary can significantly improve the situation within as little as 30 days, and deliver further enhanced benefits within 60 days.

Conclusion
There is data to suggest that each of the active components of the formulation investigated in this trial should deliver a beneficial effect in relieving different symptoms of the menopause. This open label pilot study investigated the likelihood that combining these ingredients together might deliver enhanced benefits in a single dose presentation.

The findings of this investigation add to others which have identified the constituents in the formulation provide a therapeutic option for relieving likely individual typical and common troublesome symptoms which impact upon quality of life during the menopause.

A statistical significant improvement was identified in all menopausal symptoms assessed. However by its very nature, this open label pilot study was limited in terms of patient numbers and controlled elimination of possible confounders due to the self-assessment nature of the data collection. The trial was limited by the fact that it did not include a comparison group and was neither placebo controlled, nor double blinded.

Nevertheless, the results suggest this supplement represents a likely safe and effective first stage intervention for menopausal symptoms. A further investigation of the formulation in this condition in a double blind placebo controlled setting using the same validated instrument to collect symptom data is warrented.

References

1. Murphy SL, Xu JQ, Kochanek KD. Deaths: final data for 2010. National Vital Statistics Reports. Vol. 61, No. 4. Hyattsville, MD: National Center for Health Statistics; 2013.
2. National Center for Health Statistics. Health, United States, 2012: with special feature on emergency care. Hyattsville, MD: National Center for Health Statistics; 2013.
3. J Dratva, F. Go´mez Real, C Schindler, et al. Is age at menopause increasing across Europe? Results on age at menopause and determinants from two population-based studies Menopause: The Journal of The North American Menopause Society 2008 Vol. 16, No. 2,
4. Nelson HD. Menopause. Lancet 2008;371:760–70.
5. Gold EB, Colvin A, Avis N, Bromberger J, Greendale GA, Powell L, et al. Longitudinal analysis of the association between vasomotor symptoms and race/ethnicity across the menopausal transition: study of women's health across the nation. Am J Public Health 2006;96:1226–35.
6. Santoro N, Komi J. Prevalence and impact of vaginal symptoms among postmenopausal women. J Sex Med 2009;6:2133–42.
7. Kravitz HM, Zhao X, Bromberger JT, Gold EB, Hall MH, Matthews KA, et al. Sleep disturbance during the menopausal transition in a multi-ethnic com- munity sample of women. Sleep 2008;31:979–90.
8. Bromberger JT, Schott LL, Kravitz HM, Sowers M, Avis NE, Gold EB, et al. Longitudinal change in reproductive hormones and depressive symptoms
9. Wyatt KM, Dimmock PW, Frischer M, et al. Prescribing patterns in premenstrual syndrome. BMC Womens Health. 2002;2(1):4.

10. Barnes J, Ernst E. Traditional herbalists' prescriptions for common clinical conditions: a survey of members of the UK National Institute of Medical Herbalists. Phytother Res. 1998;12:369–371.
11. Deutch B. Menstrual pain in Danish women correlated with low n-3 polyunsaturated fatty acid intake. Eur J Clin Nutr. 1995;49:508–516
12. Deutch B. Painful menstruation and low intake of n-3 fatty acids. Ugeskr Laeger. 1996;158:4195–4198. Danish.
13. Harel Z, Biro FM, Kottenhahn RK, Rosenthal SL. Supplementation with omega-3 polyunsaturated fatty acids in the management of dysmenorrhea in adolescents. Am J Obstet Gynecol. 1996;174:1335–1338
14. Wakeman. M An open-label pilot study to assess the effectiveness of krill oil with added vitamins and phytonutrients in the relief of symptoms of PMS Nutrition and Dietary Supplements 2013:5 17–25
15. Vin˜ a, J.R., Sa´ez, G.T., Vin˜ a, J., 1989. The physiological functions of glutathione. In: Miquel, J., Quintanilha,
16. T., Weber, H. (Eds.), Handbook of Free Radicals and Antioxidants in Biomedicine, 2. CRC Press, Boca Raton, FL, pp. 121–132.
17. Miquel, J., Weber, H., 1990. Aging and increased oxidation of the sulfur pool. In: Vin˜a, J. (Ed.), Glutathione: Metabolism and Physiological Functions. CRC Press, Boca Raton, FL, pp. 187–192
18. Harding, J.J., Blakytni, R., Ganea, E., 1996. Glutathione in disease. Biochem. Soc. Trans. 24, 881–884.
19. Chen, T.S., Richie Jr., J.P., Nagasawa, H.T., Lang, C.A., 2000. Glutathione monoethyl ester against glutathione deficiencies due to aging and acetaminophen in mice. Mech. Ageing Dev. 120, 127–139.
20. Lethaby A, Marjoribanks J, Kronenberg F, Roberts H, Eden J, Brown J. Phytoestrogens for menopausal vasomotor symptoms. Cochrane Database Syst
21. Machado DG, Bettio LEB, Cuhna MP, et al. Antidepressant-like effect of the extract of rosemarinus officinalis in mice: involvement of the monoaminergic system. Prog Neuro-Psychopharmacol Biol Psychiatry. 2009;33:642–650.
22. Yildirim, Basak, et al. "The effects of postmenopausal Vitamin D treatment on vaginal atrophy." *Maturitas* 49.4 (2004): 334-337
23. Anunciato, T.P., da Rocha Filho, P.A., 2012. Carotenoids and polyphenols in nutricosmetics, nutraceuticals, and cosmeceuticals. J. Cosmet. Dermatol. 11 (1) 51– 54.
24. Schneider HPG and Behre HM: Contemporary evaluation of climacteric complaints: Its impact on quality of life In: *Hormone replacement therapy and quality of life. The Parthenon Publishing Group* Edited by: *Schneider HPG. Boca Raton, London, New York, Washington*; 2002:45-61.
25. Kupperman HS, Blatt MHG, Wiesbader H and Filler W: Comparative clinical evaluation of estrogen preparations by the menopausal and amenorrhoea indices *J Clin Endocrinol* 1953, 13:688-703.
26. Kupperman HS, Wetchler BB and Blatt MHG: Contemporary therapy of the menopausal syndrome *JAMA* 1959, 171:1627-1637.
27. Potthoff P, Heinemann LAJ, Schneider HPG, Rosemeier HP and Hauser GA: Menopause-Rating Skala (MRS): Methodische Standardisierung in der deutschen Bevölkerung *Zentralbl Gynakol* 2000, 122:280-286.
28. Heinemann K, Assmann A, Möhner S, Schneider HPG and Heinemann LAJ: Reliabilität der Menopause-Rating-Skala (MRS). Untersuchung für die Deutsche Bevölkerung *Zentralbl Gynakol* 2002, 124:161-163.
29. Schneider HPG, Heinemann LAJ, Rosemeier HP, Potthoff P and Behre HM: The Menopause Rating Scale (MRS): Reliability of scores of menopausal complaints *Climacteric* 2000, **3:**59-64.
30. Hill K. The demography of menopause. Maturitas. 1996;23:113–127
31. Huang AJ, Grady D, Jacoby VL, Blackwell TL, Bauer DC, Sawaya GF. Persistent hot flushes in older postmenopausal women. Arch Intern Med.2008;168:840–846.
32. Barnes PM, Powell-Griner E, McFann K, Nahin RL. Complementary and alternative medicine use among adults: United States, 2002. Adv Data.2004;27:1–19.
33. van der Sluijs CP, Bensoussan A, Liyanage L, Shah S. Women's health duringmid-life survey: the use of complementary and alternative medicine by symptomatic women transitioning through menopause in Sydney.Menopause. 2007;14:397–403.
34. Gold EB, Bair Y, Zhang G, et al. Cross-sectional analysis of specific complementary and alternative medicine (CAM) use by racial/ethnic group and menopausal status: the study of women's health across the nation (SWAN). Menopause. 2007;
35. Légaré F, Stacey D, Dodin S, et al. Women's decision making about the use of natural health products at menopause: a needs assessment and patient decision aid. J Altern Complement Med. 2007;13:741–750.15
36. Statement of Interest. The author declares no conflict of interest