Chapter 5

Treatment for menopausal symptoms

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Women in menopausal transition have estrogen deficiency that is commonly associated with high FSH and LH levels. Declining estradiol (E_2) concentrations induces various menopausal problems, for example hot flushes, nights sweating, and sleeps disturbance, etc. Management of menopausal symptoms depends on their severity, standard of treatment in each medical setting, and women's expectation. Factual information from a systematic review showed that the frequent and severe of the symptoms in menopausal was different from racial groups.[1] There are many treatment choices for menopausal symptoms: hormonal therapy, behavioral therapy that includes exercise, nutrition, dietary and phytoestrogen consumption, and life style modifications, to name just a few.

5.1 Global consideration

The medical interventions for perimenopausal management have 2 overall objectives. The short-term objective is to alleviate turbulent symptoms and long run goals are to aim to support any programs for healthcare prevention. Problems of this prevention are acquainted. Particularly to embrace birth control, stop of smoking, management of bodyweight and alcohol consumptions, interference with cardiovascular diseases and osteoporosis, to maintain mental health wellbeing (include sexual behavior), screening for cancer, and cure for urologic symptoms.[2] Actually, menopausal transition could be a stage during a woman's life throughout that they need a chance to cut back the chance factors so as to maximise the standard of their remaining life.[3] A type of treatments are researched in RCTs; randomised clinical trials for menopausal problems, such as oestrogen, usually together with progestin. Alternative studied treatments embrace numerous hormone, antidepressant, isoflavone and alternative phytoestrogen, botanical, acupunctures, and lifestyle modifications.[4]

5.1.1 Hormonal Therapy

Patients who reported hot flashes, problem to sleep, and/or alternative problems related to menopausal transitions, hormone medical aid could be a viable choice. When patients intend to treat their symptoms at least 6 months, follicle stimulating hormone and luteinizing concentration are considerably to reduce. Hormone therapy can alleviate symptoms and instantly improve their quality of life (QOL), it will conjointly cut back the risks for osteoporosis and CVD (cardiovascular disease). These are 2 majors cause for morbidity and mortality in aging women.[3]

(1) Estrogen

Since the year 2002, clinicians have suggested HRT(hormone replacement therapy) is a primary choice for the treatment of general menopausal symptoms and for the first prevention of CHD (coronary heart diseases) in menopausal women.[5, 6]In the report of WHI(Women's Health Initiative) reportable that women aged 50s-59s (treated conjugate equine oestrogens; CEE), required less frequent coronary revascularization than those within the placebo group.[7]In addition, oestrogen (sometime combine progestin), is by far the most effective systematically for hot flashes and nights sweating. Low dose oestrogen (conjugated equine oestrogen ≤ 0.3 mg of, oral micronized oestradiol ≤ 0.5 mg, transdermic oestradiol≤ 5

μg of, and/or ethinyloestradiol ≤ 2.5 μg) show an effective treatment, though some participants need better doses to relief hot flashes.[4]

The NIH study showed that oral oestrogen, and sometime combined progestin, and a range of transdermal and vaginal oestrogen preparation is helpful for a few uro-genital problems, like dry vagina and pain from sexual intercourse. Oestrogen has conjointly been found to enhance sleep disorders and increase QOL. Astonishingly, the uses of oestrogen for the cure of mood problems are debatable. This is also very low evidence that represented that oestrogen can treat mood problems in menopausal women.[4]

The risk to combine estrogen/progestin (Prempro) compared with placebo showed that the health risks from hormone therapy were outweighed of the advantages. Preliminary information presented nearly 26 % increase RR; relative risk of carcinoma and enhanced RR of coronary heart disease.[8] From this proof, the AHA (American Heart Association) suggested to resist combining of oestrogen and progestogen for the 2nd CHD prevention. Accordingly, the USA Preventive Service Task Force suggested that women are against to use hormone replacement therapy completely for the aim of chronic problems prevention.[9-11] The first discontinuance from WHI's oestrogen/progestins trial produced an intend media and public response of the potential damage from hormone replacement therapy. It was a rapid 80% decrease in prescription for hormone replacement therapy from 2002 to the last quarter of 2004.[12, 13] Afterward, in March 2004, the WHI study was use estrogen alone arm in the trial. This trial was conjointly stopped early, once analyzes an information that showed an enhance risks of stroke and not totally profit for CHDs.[14] Furthermore, oestrogen medical care with similar dose to 0.625 mg. for conjugate equine oestrogen. It will increase a chance for serious un-wellness event, particularly stroke, deep phlebothrombosis, and embolism. Oestrogen once combine with medroxy progestogen acetate will increase the chance of coronary events and carcinoma in breast. The enhanced risk for both illness events began to emerge within 12 months. Risk for stroke began to rise after used 2 years. Risk for breast cancer began to rise when using between 3 – 4 years. Though specialists theorized a long adverse effect that related to low dose oestrogen are lower. Disadvantage and advantages were not seemed to know. Risks and benefits analysis are necessary whether hot flashes and night sweating are severe and harmfull on everyday lives. Women with these situation are also willing to assume larger risk for reducing these problems.[4]

(2) Androgens (Testosterone)

Some proof showed that oral testosterone together of oestrogen will improve sexual desire. In distinction, there have been no other advantages for vaginal dryness or sleeps disturbance. Additionally, transdermal testosterone in women who experienced to surgery for climacteric conjointly showed to improve sexual dysfunctions. The adverse affects of testoseterone for the treatment of skin disorder, hirsutism, and overweight. For the long run risks from the using testosterone haven not been researched in this population.[4]

(3) Dehydroepiandrosterone

A few prospective studies of dehydroepiandrosterone (DHEA) recommend that it is potential profit for the cure of hot flashes and reduced sexual desire.[4]

(4) Tibolone

Tibolone, an artificial steroid with comparatively weak hormonal activity, have used to cure vasomotor symptoms (hot flashes), sleep disturbance, sexual dysfunctions and to prevent osteoporosis nearly 20 years. Report from the US. Researches, exploitation tibolone combined with oestrogen, showed similar effectiveness for hot flashes and sexual desire. An adverse affects from tibolone embrace pains, gained weight, and headaches. It is still vague if tibolone use is related to female internal reproductive organ haemorrhage. The long-run affects from tibolone, significantly regarding to breast cancer, CVDs, and also osteoporotic fractures reduction, are nor reported.[4]

5.1.2 Non-hormonal therapy

(1) Natural Hormones

Hormones for nature can treatments by using combined compounds that contain steroid in varied doses. These steroids might embrace oestrone, oestradiol, oestriol, DHEA, progestrogen, pregnenolone, and androgenic hormone. There is inadequate information to describe an advantages and AEs (adverse effects) from those compound.[4]

(2) Antidepressants

The treatment form antidepressants for hot flushes have show mix results. Agents of paroxetine and venlafaxine might moderately decrease hot flashes and improve QOL for symptomatic women undergoing normal climacteric women, additionally for breast carcinoma survivors. The long adverse effects of antidepressants, as well as diminished sexual desire, sleep problems, headache, and nausea, require further research.[4]

(3) Other Medications

Few RCTs reportable the effectiveness of antihypertensive drug, gabapentin, methyldopa, and belle gal as management of hot flushes, sleep disorder and/or mood symptoms. The sole obtainable study of gabapentin incontestable an improvement in flush frequency and sleep disturbance, however exhibited facet effects, like drowsiness, dizziness, rash, and peripheral swelling. Antihypertensive drug was effective in reducing flush frequency in studies of carcinoma survivors, however was related to sleep disorder.[4]

(4) Isoflavones and Other Phytoestrogens

Isoflavones and other phytoestrogens are used in menopausal women in many countries. However, it is difficult to evaluate their effects, as there is no standard manufacturing process in those countries. Many studies of mixed soy suggest that they might have some affects on hot flushes, but the majority in these studies do not show benefit. Adverse events and long-term side effects remain unknown.[4]

In conclusion, hormone replacement therapy remains distinguished for the treatment of an uncommon menstruation, vagina dryness, vasomotor problems, and/or weakened sexual desire. Clinicians would considerably additional doubtless than patients to use hormone replacement therapy for climacteric problems. Feminine clinicians were additional doubtless than men to mention those care patterns; modified as a results of the WH's study.[15]

5.1.3 Complementary and alternative therapy (CAM)

In recent years, to control the climacteric problems has received more attention as a consequence not only the growing interest in women's health but also the higher number of women entering the climacteric years is included. Concern and dislike of potential facet effects and long risks of hormone replacement medical care, discontentment with standard medication in conjunction with the assumption that "natural" products are safer, and also any findings from the WHI's study had contribute an exponential increase within the acceptance and use of complementary and alternative medical care for climacteric symptoms.[16] The scientific literature has been classified beneath the heading "nutritional/supplements", "herbal remedies", "homeopathic remedies", and/or "physical approaches". Some Scientifics proved the protection and effectiveness from other cares throughout climacteric were not covered. However, the strongest proof suggested that to rise phytoestrogens favour as isoflavones in soy product concentrations would be benefit..[17]

Generally, studies with the benefits of botanicals were shown in different approaches.[4]

(1) Botanics

The studies of botanic product menopausal problems have had inconsistent results. For natural variability in botanicals, methods to extracts and produce, together with additional product additives has impeded a methodical study of their effectiveness. However, the NIH study[4] has summarized the following botanical effects:

(1.1) Black cohosh (*Actacearacemosa* or *Cimicifugaracemosa*)

Black cohosh, the most studied botanical product, has had an honest safety record over a few years. Some cautions are raised concerning attainable adverse effects of Cimicifugaracemosa on the liver, however reports of adverse events stay unclear.[4] Its effectiveness within the treatment of climacteric symptoms is debatable, and additional studies are required.[18] Because it is often used in conjunction with other botanicals, evaluation of adverse events is difficult. The seriousness of some adverse events suggests that further investigation is urgently needed.[22]

(a) Intoxicant (*Piper methysticum*) had proven to be benefit to reducing anxiety, however no proof substantiates it's effective to hot flushes. Sadly, intoxicant has been associated with liver injury and a warning to patients and providers concerning potential dangers has issued by the United State Food and Drug Administration.[4]

(b) Trifoliumpratense leaf (*Trifolium pretense*): contain any compounds of phytoestrogen that are acted as a weakening of oestrogen. Moreover, researches recommend that it was not effective to reduce hot flushes.[4]

(C) Root of Dong quai (*Angelica sinensis*): wide employed in several menopausal problems, however it was not effective against hot flashes. Its interaction with anticoagulant medication might cause haemorrhage complications.[4]

(1.2) Root of Ginseng (*Panaxquinquefolius*) might improve QOL outcomes, like well-being, mood, and sleep, however it is ineffective within the treatment of hot flashes.[4]

(2) Behavioral Interventions

Behavioral interventions, which have few adverse effects, are an essential area that should be studied as a means to manage menopausal symptoms. To date large, well-controlled studies have not been able to demonstrate the effectiveness of behavioral interventions. However, several small studies have shown that:

• Exercise improved the quality of life (QOL) but did not affect other menopause associated symptoms, such as vasomotor symptoms or vaginal dryness.[4, 19]

• Health education improved knowledge concerning climacteric and its associated those symptoms but did not amendment the problems themselves.[4, 19]

• Paced-respiration (slow and deep respiratory requiring training) for hot flashes presented a promise in a few cluster of participants.[4, 19] A few researches have evaluated behavioural ways for assuaging hot flushes. Once research was compared paced-respiration (slow and deep breathing) by progressive muscle relaxation techniques or non-therapeutic α-wave electroencephalogram training program (control group) in 33 post-menopausal women.[20] Paced-respiration coaching 16 weeks considerably to reduce frequency of hot flashes up to 39%; progressive muscle relaxation technique coaching and also the management of intervention have not vital impact. During a newer research with a similar investigator, 24 post-menopausal women (minimum 5 times of hot flushes daily) were at random assignment to either paced-respiration or training program management.[21] Paced-respiration attenuated hot flashes considerably by 44%.; no modification occurred within the management cluster. Adverse effects were not noted. Another randomised 7-weeks trial of relaxation responses recruited 45 participants (women: 33 completed the study), aged 44s-66s, and were experiencing a minimum of 5 times hot flashes daily. Participants were at random assigned to a relaxation responses cluster, reading cluster, or a symptom charting (control) cluster. In the relaxation cluster were educated relaxation responses technique and asked to observe 20 minutes daily; the browsing cluster read leisure material for 20 minutes daily. Hot flashes frequency was remained unchanged, however the severity of hot flushes was reduced considerably solely within the relaxation cluster.[22] But, for gentle hot flushes, lifestyle-related methods (keeping the core temperature cool, collaborating in regular exercise, and exploitation paced-respiration) has shown some effectiveness, while not AEs.[23] What is more, the amount of hot flashes and alternative vasomotor symptoms will be reduced considerably by applied relaxation.[24, 25]

Making a decision for women regarding the management of climacteric symptoms needs equalization the potential advantages against some risk. Women with a high risk of serious outcome; with the utilization of oestrogen are more severe from previous breast cancer, and/or elevated risks of breast or female internal reproductive organ cancer on the premise of genetic factors, and people who have high risk for CVD. Such women is also significantly inspired to hunt non-hormonal treatments for menopausal symptoms.[4]

5.2 Relaxation technique for treating menopausal symptoms

Women with post-menopausal hot flashes, who learned and practiced applied relaxation for 6 months, had a mean of 73%reduction within the frequency of flashes.[26] In another study of applied relaxation and oral oestradiol treatment for vasomotor symptoms, the amount of hot flashes in 24 hours reduced considerably over time in those that follow applied relaxation for 12 weeks.[25]

The study of Yoga and psychological relaxation for treating climacteric problems reportable that this method considerably reduced the intensity of questionnaire-rated of total climacteric problems, hot flushes in daily life; and improve sleeps potency and quality.[27]

Cognitive-behavioral intervention (eight weekly sessions, 2 hours each, involving relaxation, psychological feature techniques, exercise, and diet) for menopausal symptomatology showed a major reduction of most physical and psychological symptoms, and a rise in quality of life within the treatment cluster.[28]

Using interview and form, an evidence-based review of 90 minutes “restorative yoga” training for menopausal symptoms reportable decline within the intensity and frequency of hot flashes after treatment 8 weeks.[29] The research on RCT in postmenopausal women (examine sleep quality) entered 164 women into 2 groups. Results found that participants in Yaga group were reduced intensity within 4 months, as same as in a moderate-intensity walking group, or a wait-list management group. There have not vital interventional effects statistically of any treatments on either total sleeps qualities or individual’s sleep quality domain.[30]

5.3 Supporting research

(1) The study entitled “Relaxation for perimenopausal and postmenopausal symptoms (Appendix B).

Potential risks, associated with HRT (hormone replacement therapy), have complicated for the treatment of menopausal problems. Other pharmaceuticals and self-care strategies, such as relaxation techniques, are alternative options.

The study purposed to examine the effect of relaxation method as a therapy for hot flushes, nights sweat, and associated disturbances of sleep in women during peri- and postmenopausal period. Searching strategies used the following electronic bibliographic databases to identify randomized controlled trials (RCTs) as reported in varied databases). Searching by hand in relevant journals and printed abstracts’ conference were performed; ILACS, Clinical Study Results, PubMed, and OpenSIGLE for grey literature reports in Europe, using the same search terms. Searches included dates up to January 21st; 2013.The inclusion criteria were RCTs, which compared any type of relaxation interventions with no treatment or other therapy (except hormones) for hot flashes, night sweats, and sleep disturbances in peri- and postmenopausal women. Two reviewers collected and analyzed data. For included studies, two reviewers were combined by using a random effect model, if appropriate, to calculate pooled mean differences and 95% confidence intervals.

There were 540 abstracts that met the following criteria of searching terms; relaxation, menopausal symptoms, and clinical trials. Only 13 relevant abstracts were obtained as full text articles. These articles were read in more detail to decide whether to include them in this review. Five studies were excluded because they were quasi-experimental studies. Only eight studies were assessed in detail. Four studies were excluded because three were pseudo RCTs and one was a duplicate of another study. In all, only four studies were eligible for inclusion (270participants): two studies compared relaxation with electroacupuncture, one study compared relaxation with control (α-wave electroencephalographic biofeedback), and one study compared relaxation with no treatment. Only two studies (relaxation versus electroacupuncture) reported outcomes that could be combined in a meta-analysis. The report showed no significant difference of treatment effect between relaxation and acupuncture; Mean Difference (MD) of change in hot flushes frequency 0.05, 95%CI: -1.33 to 1.43, two studies, 72 participants, I^2=0%; this evidence very low quality). Nor were there any difference significantly between 2 interventions (severity in hot flush), calculated by the Kupperman Index (MD -1.32, 95% CI -5.06 to 2.43, two studies, 72 participants, I^2=0%; very low quality evidence). Results of these two studies were consistent. The other two studies reported no significant difference in hot flushes between relaxation compared with control or no therapy. All studies had small sample sizes, and risk of bias had a low or unclear. No study reported night sweats, sleep disturbances associated with night sweats, or adverse effects as an outcome.

In conclusion, the existing studies provided inadequate proof to evaluate the effect of relaxation techniques as a therapy of vasomotor symptoms. Nor was there sufficient evidence to determine if the treatment was more effective than acupuncture. Relaxation was not reduced the frequency of hot flushes. No included study reported night sweats and sleep disturbances as the outcomes. No data were reported on adverse events. It was very low evidence quality, with winy sample sizes and moderate methodological quality of the included studies. However, relaxation techniques require a long and continuous practice to achieve the treatment effect and subjects' compliance can be a problem. No evidence was found to indicate whether these interventions differ in effectiveness.

(2) The study entitled "Effectiveness of a modified version of applied relaxation in treatment of perimenopausal and postmenopausal symptoms (Appendix C)

Nowadays, awareness of the risks related to hormone medical care for menopausal symptoms has inflated. Various treatments to alleviate menopausal symptoms are, therefore, usually needed. The applied relaxation (AR) technique has established to achieve success for symptom improvement; however it needs participation in 12 weekly classes. This study planned to determine the effectiveness of a changed relaxation version (MR) of AR for treating hot flushes, night sweating, and sleep disturbances. The study was a parallel, randomized, open-label investigation of MR versus AR, conducted over 12 weeks in peri-* and postmenopausal women. The investigation was administrated at Menopausal Clinic, Mahasarakham Hospital in Northeastern, Thailand from July 2011 to January 2012. The

Ethics Committee of Mahasarakham Provincial Hospital were approve the study, and every one participants informed consent.

We recruited 105 peri- and postmenopausal women who visited the climacteric clinic at Mahasarakham Provincial Hospital. Of those, 88 women experiencing hot flashes, night sweats, or sleep disturbances were probably eligible, and 81% selected to participate. Participants were at random assigned to MR or AR cluster. The MR cluster (n=36) received one session of (MR) coaching and also the AR cluster (n=35) received typical 12-week coaching. They were educated to observe the methods daily at home for 12 weeks. Two main outcomes were the severity and hot flashes frequency, night sweating, and sleep disturbances. Participants in both groups were kept a specific record of intensity and frequency of their symptoms in record book. A research nurse recoded information employing a standardized medical history form. Most participants (67/71, 94.4%) adhered to the protocol. The trainers contacted participants by telephone call every week to answer queries, resolve any problems, assess symptoms, and monitor AR/MR practice. Outcome variables enclosed the modification in severity, employing a rating scale score, and alter in frequency of hot flushes, night sweating, and sleep disturbances. Data analysis was conducted as “intention-to-treat,” with all participants enclosed within the analysis. Descriptive statistics were applied to summarize baseline demographics and clinical characteristics. Chi-square ($\chi 2$) and Student’s t-tests were accustomed assess differences between groups, as acceptable. The Wilcoxon rank-sum was accustomed assess differences within the rating scale variables. Statistical significance set at a p-value <0.05 (two-tailed).

All participants completed the12-week intervention. Total severity scores reduced in both groups after 12 weeks; however there were no difference between groups. For intensity (severity) score of hot flashes within the MR cluster reduced over that within the AR cluster. The severity scores for night sweats and sleep disturbances reduced in each groups. Frequency of hot flashes, night sweating, and sleep disturbances were conjointly reduced in both groups. In conclusion, a shorter changed version of the AR was equally effective or slightly higher than the standard AR for reducing hot flashes, night sweating and sleep disturbance in peri- and postmenopausal women.

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