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Alternatives to Hormone Replacement Therapy in Postmenopausal Women

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Authors' contributions

Author MN desgined the study and wrote the manuscript. Author KS revised and edited the manuscript. Author BS managed literature search.

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Review Article

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ABSTRACT

Substantial number of postmenopausal women suffers in silence. They experience vasomotor symptoms, sleep disturbances, atrophic changes in the genital and urinary systems and lack of sexual desire. The fear, side effects and contra indications of oestrogen discourage hormone replacement therapy.

Life style modification with change in dietary habit, regular exercise, cessation of alcohol and smoking can help them immensely. Tibolone, Selective oestrogen receptor modulators (SERMs), Antidepressants like Venlafaxine, th Alpha 2 agonists like clonidine, carbapentine and various supplements are frequently prescribed. Available alternatives and their merits are discussed.

Keywords: Postmenopause; hormone replacement; lifestyle; tibolone; SERMs.

1. INTRODUCTION

Women in post menopausal age group may suffer from circulation index (hot flushes, sweating, palpitation, dizziness), nervosity index (irritability, headache, anxiety, depression, sleep disturbances, aches and pains) atrophic changes in the genito-urinary tract and decreased sexual desire. They are prone to osteoporosis and cardiovascular disease.

The important feature of menopause is lack of oestrogen. The oestrogen level decreases to

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20% of the premenopausal level. The main source of oestrogen in postmenopausal women is osterone which is only one sixth of the potency of oestradiol. The mean oestradiol level prior to menopause is 100 - 200 pg/ml and postmenopausal oesterone level is 45 pg/ml.

The Menopause is essentially a clinical diagnosis. The cessation of menstrual period for more than 12 months, postmenopausal symptoms, 17 beta oestradiol level is less than 74 pmol/l and FSH level is more than 35 miu/l are features of menopause.

Premature Menopause: Menopause in a woman aged below 40 years.
Early Menopause: In a woman aged 50 years to 59 years.
Late Menopause is in a woman aged 60 years and over.
Surgical menopause is a result of surgical removal of both ovaries in a woman.

Medical menopause occurring as a result of permanent damage to both ovaries in a woman following either chemotherapy or radiotherapy. The menopause occurs at a median age of 51 years, varying from 40-58 years [1].

Women are reluctant to take hormone replacement therapy (HRT) due to fear, side effects and contra indications of oestrogen therapy. Despite recent encouraging data regarding the safety of traditional HRT women and their primary care practitioners continue to be concerned about the purported risks, particularly to the breasts and cardiovascular system [2].

Are there alternatives to alleviate their postmenopausal symptoms other than the conventional hormone therapy?

2. DISCUSSION

This article is an attempt to consider the merits of alternatives to HRT.

Example:

I. LIFE STYLE MODIFICATIONS
II.MEDICATIONS
(a)Tibolone (Livial)
(b)Selective estrogen receptor modulators (SERMs)
(c) Drugs to prevent vasomotor symptoms
III. COMPLEMENTARY THERAPIES
IV. COMPLEMENTARY PROCEDURES

3. LIFE STYLE MODIFICATIONS

Lifestyle modification should be considered as an integral part of menopausal management [3]. Reduction of weight, avoid or reduction of smoking and alcohol and regular exercise can substantially help them. Active women found to have less post menopausal symptoms [4] Exercise improve mild to moderate depression and anxiety. It reduces the blood sugar level and facilitates sleep.

Aerobic exercise like jogging, walking, swimming and cycling are cardio protective and improve the health and quality of life. They are claimed to reduce vasomotor symptoms. Weight bearing exercise like jogging, walking, tennis and netball act on feet. It helps to maintain the body mass and prevent osteoporosis. Flexibility exercise like yoga mobilises and stretches the joints, ligaments, muscles and tendons. Mild form of exercise also beneficial in reducing vasomotor symptoms and improving the psychological wellbeing.

It must be cautioned that not all types of physical activities improve the symptoms. Irregular high impact vigorous exercise can make symptoms worse. For a plant, one cup of water a day is better than a bucket of water a month.

Light weight loose clothes, sleeping in a cooler room, reducing the stress and make the life happy may reduce the intensity and number of hot flushes.

Over stress can cause gastric problems, headache, sleep disturbances and mood disturbances. Meditation, yoga, hypnosis, acupuncture regular and relaxation exercise may help to overcome stress. Stress management books and therapists are helpful. Mindfulness training and cognitive behaviour therapy can reduce stress.

However, evidence from randomised controlled trials concerning the effects of aerobic exercise on vasomotor and other menopausal symptoms is limited. Aerobic exercise can improve psychological health and quality of life in vasomotor symptomatic women. In addition, several randomised controlled trials of middle-aged/menopausal-age women have found that aerobic exercise can result in significant improvements in several common menopause-

related symptoms like sleep disturbances and mood changes. Low intensity exercise such as yoga may be beneficial in reducing vasomotor symptoms and improving psychological wellbeing in menopausal women [5].

3.1 Change of Dietary Habits

You are what you eat and what you read.

When a woman grows older she requires less energy and the food intake should also be reduced. If the same amount of food is continued, obesity can occur. Women should reduce fast food which has high quantity of salt, sugar and saturated fats. (Three bad Ss) They should increase the consumption of vegetables, fruits, whole grains, lean meat and fish. Virgin coconut and olive oil, nut and seeds are recommended. These can reduce the risk of developing diabetes and atherosclerosis Spicy foods, caffeine should be reduced.

4. MEDICATIONS

(a)Tibolone(Livial)

Tibolone is a synthetic hormone derived from Mexican yam. When taken by mouth it brakes into components that act similar to oestrogen, progesterone and testosterone.

Oestrogen like activity prevents hot flushes, osteoporosis, vaginal atrophy and dryness. At the same time it also increases the incidence of breast cancer, deep vein thrombosis and endometrial hyperplasia. Progesterone like activity reduces the risk of endometrial hyperplasia. Testosterone like activity increases the sexual desire and improves mood changes. It also decreases the plasma high density lipoprotein cholesterol (HDL), triglycerides and lipoprotein and may increase blood fibrinolytic activity.

The 2.5 mg dose appeared to be the optimal dose for relieving hot flushes, sweats and other climacteric complaints.

Mammographic density has not shown statistically significant increase compared to placebo with 2.5 mg daily dose. The Million Women Study (MWS) has identified a significant increase in the risk of breast cancer in association with use of the 2.5 mg dose. However, a study using the General Practice Research Database (GPRD) did not show an increased risk. In clinical studies mammographic density is not statistically significantly increased in women treated with Livial 2.5 mg daily compared to placebo but a trend to higher mammographic density was noted for Livial 2.5 mg daily. However in a known, past or suspected breast cancer – Livial increased the risk of breast cancer recurrence in a placebo-controlled trial [6].

The bone mineral density (spine, femoral neck, trochanter and Ward's, and distal radius) had significantly increased in 75 women treated with 2.5 mg Tibolone for 2 years compared to placebo.

Contraindications are similar to that of oestrogen therapy such as past or suspected breast cancer, endometrial hyperplasia and cancer, Previous or current venous thromboembolism and active liver disease.

Tibolone is ideal for women above 60 years of age when they are intolerant and contraindicated for other medicinal product.

Tibolone increases the risk of breast cancer but not to the extent of oestrogen and progesterone. Limited data do not suggest an increased risk of venous thromboembloism and there are insufficient data to draw a conclusion on the risk of cardio vascular disease with tibolone. 13 Tibolone is associated with an increased risk of stroke particularly in older women, and an increased risk of endometrial cancer. It may enhance the effects of anticoagulants such as warfarin [7].

(b) Selective estrogen receptor modulators (SERMs)

SERMs act on oestrogen receptors. They are selectively agonists in some tissues and antagonists in some cells. Therefore they specifically stimulate and inhibit oestrogen like action in different areas. Raloxifene, Lasofoxifene and Ospemifene are agonist at bone and prevent osteoporosis. They are antagonist at breast and prevent breast cancer.

SERMs prevent osteoporosis and invasive breast cancer.

Raloxifene is commonly prescribed. The daily oral dose is 60 mg. In a three-year study involving some 600 postmenopausal women,

raloxifene was found to increase the bone density and lower LDL cholesterol and no endometrial hyperplasia. Raloxifene does not reduce the risk of coronary heart disease [8].

Lasofoxifene oral dose of 0.5 mg/day was effective in the prevention of both vertebral and nonvertebral fractures in postmenopausal women with osteoporosis. Ospemifene improves dyspareunia [9].

SERMs do not improve hot flushes. The risk of deep venous thrombosis is slightly increased with SERMs. Leg cramps and swelling are frequent complaints.

Daily therapy with raloxifene increases bone mineral density, lowers serum concentrations of total and low-density lipoprotein cholesterol, and does not stimulate the endometrium. The increase in bone mineral density at most sites was greatest in the group that received 150 mg of raloxifene per day; however, in the total hip the greatest increase was in the 60-mg group [10].

(c) Drugs to prevent Vasomotor symptoms

Hot flushes are the most common symptoms of menopause. Hot flashes have been reported in up to 70% of women undergoing natural menopause and in almost all women who have undergone surgical menopause [11].

They are mostly during the first year of menopause and last for 1-5 years in 90% of women but may persist as long as 15 years in few women [11]. They are described as sudden feelings of warmth (on the chest, face and neck), often associated with perspiration, palpitations and anxiety, which are variable in frequency, duration and severity (lasting less than 5 minutes). They can be triggered by warm environments, hot food or drinks and stress, and can interfere with activities or sleep.

The symptoms are more severe in those women who have had a surgically induced menopause. Modifiable and non modifiable risk factors for hot flashes should be evaluated. Modifiable factors that have been shown to increase the risk of occurrence of hot flashes include cigarette smoking [12] body mass index >30 kg/m_2 [13] and lack of exercise [14,15]. Non modifiable risk factors include maternal history, menopause at younger than 52 years of age, and abrupt menopause—induced by a surgical procedure [16], chemotherapy, or irradiation. Approximately 65% of patients with a history of breast cancer have hot flashes [17] and adjuvant therapy with tamoxifen or tamoxifen plus chemotherapy is associated with substantial worsening of menopause-related symptoms [18].

(i) Alpha-2 agonists (Clonidine)

Clonidine is a centrally acting. α_2-adrenergic agonist. It was widely prescribed to alleviate vasomotor symptoms. The trials show contradictory reports.

A double-blind randomized controlled trial using oral clonidine showed no evidence for hot flush reduction [19].

A systematic review and meta-analysis confirmed a marginally significant benefit of clonidine over placebo; however, the effects of clonidine were not as great as those of estrogen, and adverse effects may restrict the use of clonidine for many women [20]

The effects of clonidine 0.05 mg twice/day versus placebo were studied in 66 postmenopausal women (mean age 47 yrs) for 8 weeks in a double-blind, placebo-controlled, crossover trial. At the end of the trial, patients randomly assigned to receive clonidine experienced statistically significant reductions of 78%, 89%, and 88% in hot-flash frequency, severity, and duration, respectively, compared with the placebo group. Three trials failed to find clonidine effective in reducing symptoms of hot flashes in post-menopausal women.

Transdermal clonidine patches (0.1 mg/24 hours) had substantially reduces the hot flushes. Side effects of clonidine such as drowsiness, dizziness, tiredness, irritable, runny or stuffy nose, sneezing, cough, sore throat, mood changes, headache, ear pain, sleep problems and nightmares; The adverse effects included rash, nausea, gastrointestinal disturbances, sedation, and dry mouth and were associated with higher dosages of clonidine (≥ 0.1 mg/day. These side effects discourage the use of clonidine in many patients.

Clonidine is the only non-oestrogen-based preparation licensed for menopausal flushing [21]. It should be used with caution in conditions including cerebrovascular disease, coronary insufficiency, heart failure and renal failure; treatment should be discontinued gradually [22].

Clonidine, 0.1 mg orally daily reduces 38%-78% compared with 24%-50% for placebo [23].

Transdermal clonidine (equivalent of 0.1 mg daily) given as weekly patches reduced 20%-80% compared with 36% for placebo [24].

Dopamine antagonists

Veralipride response in 63%-80% [25].

(ii) Selective Serotonin Reuptake Inhibitors (SSRI) and selective noradrenaline reuptake inhibitors (SNRIs)

SSRIs are antidepressant drugs. Commonly used medicines are paroxetine, fluoxetine, escitalopram and citalopram.

Venlafaxine, a serotonin and noradrenaline reuptake inhibitor (SNRI) found to be effective in reducing the intensity and frequency of hot flushes.

Evidence suggests that fluoxetine, paroxetine, citalopram and venlafaxine are effective in reducing the frequency and severity of hot flushes [26].

Fluoxetine, 20 mg orally daily had reduced 50% of hot flushes placebo reduced 36% [27] Paroxetine, 12.5-25 mg orally daily reduced 62-65% compared with 38% for placebo [28] Venlafaxine, 75 mg orally daily reduced 61% compared with 27% for placebo [29].

Most of the published studies were done on breast cancer patients. Carcinoma of the breast patients are treated with Tamoxifen and Tamoxifen causes hot flushes. 37.5 mg to 75 mg daily dose of Venlafaxine significantly reduces hot flushes.

Their mode of action is not known. These drugs do not help all the patients. If SSRI and SNRI benefit, they relieve the symptoms immediately. These patients can be prescribed for a long period. The side effects are nausea and lack of sexual desire.

Paroxetine 7.5 mg had favorable tolerability in menopausal women with moderate to severe VMS. The efficacy and safety of paroxetine mesylate, a selective serotonin-reuptake inhibitor (SSRI), were evaluated individually in three Phase 2 or 3 multicenter, double-blind, randomized, placebo-controlled trials. A total of 1,276 postmenopausal women (approximately 70% white) aged 40 years or older (median age, 54 years) with moderate to severe VMS (7−8 hot flashes/day; 50−60 hot flashes/wk) received either paroxetine mesylate or placebo at bedtime for 8 (Phase 2), 12 (Phase 3), or 24 (Phase 3) weeks [30]. The side effects are nausea and reduced sexual desire [31]

(iii) Gabapentin

Gabapentin is an antiepileptic drug. It is found to be more effective compared to placebo in relieving hot flushes. Gabapentin in a dose of 900 mg daily was found to reduce 45% in frequency and 54% reduction in severity of hot flushes [32]. The side effects are drowsiness, dizziness and fatigue.

Another randomised trial of gabapentin 600 mg versus low-dose transdermal estradiol 25 micrograms in women with moderate to very severe hot flushes showed symptom relief in both groups, but estrogen was more effective. Gabapentin, 900 mg daily in divided doses, reduction of 45% compared with 29% for placebo [33].

Gabapentin significant reductions in hot flashes with use of gabapentin in postmenopausal women [34].

SSRI, SNRI and gabapentin are not licensed for treating postmenopausal symptoms. However many practitioners continued to prescribe in the best interest of patients.

(iv) Beta-blockers

Beta-blockers were tried to treat vasomotor symptoms. It was not effective reducing the symptoms.

(v) Dehydroepiandrosterone (DHEA)

Dehydroepiandrosterone (DHEA) was initially used in the USA, where it is classed as a food supplement, for its supposed antiageing effects in postmenopausal women. Some studies have shown benefits on the skeleton, cognition, wellbeing, libido and the vagina [35].

An uncontrolled pilot study showed a modest reduction in hot flushes with DHEA [36].

However, placebo control is necessary to prove efficacy and further studies are essential.

(vi) Progestogens

Randomised studies had shown that megestrol acetate is superior to placebo in relieving vasomotor symptoms. However Women's Health Initiative study doubted the safety of progesterone. It is not advisable to prescribe to women with progesterone –receptor positive with increased risk of breast cancer. The progesterone dose required to relieve vasomotor symptoms can increase the risk of venous thrombo emblism [37].

Megestrol, 20 mg orally twice a day reduced hot flushes by 85% compared with 21% for placebo [38].

Medroxyprogesterone acetate, 20 mg orally daily reduced 73.9% compared with 25.9% for placebo [39].

Medroxyprogesterone acetate, 100 mg orally twice a day reduced 86% compared with 33% for placebo [40].

Depot medroxyprogesterone, 500 mg intramuscularly every 2 weeks reduced 86%, with no difference from 40 mg of megestrol [41].

Transdermal progesterone, 20 mg daily reduced 83% compared with 19% for placebo [42].

Transdermal progesterone, 32 mg daily had no significant effect [43].

Alternatives to Estrogen for Management of Vasomotor Symptoms Studied in Randomized Controlled Trials [44]

Placebo Reductions of vasomotor symptoms of 20%-50%.

Selective serotonin reuptake inhibitors:

Fluoxetine, 20 mg orally daily Reduction of 50% compared with 36% for placebo
Paroxetine, 12.5-25 mg orally daily Reduction of 62%-65% compared with 38% for placebo
Venlafaxine, 75 mg orally daily Reduction of 61% compared with 27% for placebo
Centrally acting a-adrenergic blocking agents

Clonidine, 0.1 mg orally daily Reduction of 38%-78% compared with 24%-50% for placebo [45]. Transdermal clonidine (equivalent of 0.1 mg daily) given as weekly patch.
Reduction of 20%-80% compared with 36% for placebo

Dopamine antagonists

Veralipride (not available in the United States) Response in 63%-80%

Gabapentin, 900 mg daily in divided doses Reduction of 45% compared with 29% for placebo [45].

Phytoestrogens

Soy: Reduction of 30% with soy compared with 40% for placebo (no significant difference in response) No significant difference at 12 weeks, although minor improvement at 6 weeks.

Black cohosh, 40 mg orally daily Equipotent to conjugated estrogen, 0.6 mg orally daily, both >placebo .No significant difference at 60 days.

Vitamin E, 400 IU orally twice a day Minimal decrease of 1 hot flash per day compared with placebo.

4.1 Vaginal Dryness

Low concentrations of oestrogen and androgens can lead to numerous symptoms including atrophic vaginitis, vaginal irritation, dysuria, dyspareunia, nocturia and frequency. Unlike vasomotor symptoms, urogenital symptoms do not diminish with time [46].

Many vaginal inert lubricants are available in Malaysia without prescription. KY Jelly /Gelle is freely available. It doesn't stain. It is water soluble and easily cleaned up. It is cheap and safe.

Arkopharma Phyto Soya Vaginal Gel, Woohoo! Water-Based Intimate Lubricant, Higher Nature V Gel (aloe vera) ReplensMD Vaginal Gel (polycarbophi) Durex Sensilube Intimate Moisturising Gel (polyacrylamide, parabens, citric acid) Femfresh Triple Action Moisturising Wash (lactic acid and moisturising bamboo extract) Pink Silicone Personal Lubricant and Yes Water-Based and Oil-Based Intimate Lubricants (flax extract and guar gum) are non oestrogen containing vaginal lubricants to relieve vaginal dryness.

Lubricants are combinations of protectants and thickening agents in a water-soluble base. They are usually used to relieve vaginal dryness during intercourse. They do not provide a long-term solution. Moisturisers may contain a bioadhesive polycarbophil-based polymer that

attaches to mucin and epithelial cells on the vaginal wall and retains water. Moisturisers are promoted as providing long-term relief of vaginal dryness and need to be applied less frequently [47].

4.2 Prevention of Osteoporosis

Osteoporosis is innocent until seen with fracture. The fracture can occur with minimal trauma or no trauma. This is a common problem of postmenopausal women.

The Woman's Health Initiative (WHI) had shown that 5 years of hormone therapy reduced the risk of vertebral and hip fractures by 34% and other fractures by 23%. This encouraged the prescription of hormone therapy and SERMs to prevent osteoporosis.

Hormone therapy is beneficial to treat postmenopausal symptoms and prevent osteoporosis but, they should not be used for the sole purpose of prevention of osteoporosis.

The following measures are useful to prevent the osteoporosis Diet to include calcium 1000-1200 mg and vitamin D 800 i.u. daily.

Regular weight bearing and muscle strengthening exercise. Weight-bearing exercise (in which bones and muscles work against gravity as the feet and legs bear the body's weight) includes walking, jogging, stair climbing, dancing and tennis.

Muscle-strengthening exercise includes weight training and other resistive exercises, such as yoga, Advise on reduction and cessation of smoking and alcohol. The use of tobacco products is detrimental to the skeleton as well as to overall health.

Alendronate 5 mg daily, Risedronate 5mg daily and Zoledronic acid 5mg intravenous infusion once in two years are the current recommendations to prevent osteoporosis in postmenopausal women.

5. COMPLEMENTARY THERAPIES

Complementary therapies and alternate medicines are widely published in the electronic media. Their safety and efficacy had not been well established.

5.1 Botanicals

Many plant products are in practice. Their benefits are not proven. Herbs may contain many chemical substances and their effects are not well studied.

Herbal products may interact with other medicines. Some products do not adhere to the manufacture regulations. This may also contain toxic ingredients.

There are no recognised international criteria for the design of clinical trials of alternative therapies. Herbs may contain many chemical compounds and their individual and combined effects are unknown.

(i) Phytoestrogens: soy and red clover

Phytoestrogens are plant substances with similar effects of oestrogens. Red clover extracts, dietary soy, soy extracts are some of the popular phyto oestrogens. The most important groups are called isoflavones and lignans. The major isoflavones are genistein and daidzein. The major lignans are enterolactone and enterodiol. Isoflavones are found in soybeans, chickpeas and red clover, and probably in other legumes (beans and peas). Oil seeds such as flaxseed are rich in lignans, which are also found in cereal bran, whole cereals, vegetables, legumes and fruit.

Japanese take high quantity of Phytoestrogens and the vasomotor symptoms are relatively less among them. However studies found no difference overall in the frequency of hot flushes between red clover extract and placebo (weighted mean difference –0.57, 95% CI –1.76 to 0.62).

Phytooestrogen has oestrogenic action. Large study of red clover and isoflavone had shown no increase in breast cancer risk in patient with strong family history.

5.2 Soy

Reduction of 30% with soy compared with 40% for placebo (no significant difference in response) [48].

A systematic review of 30 randomised trials (lasting at least 12 weeks and involving a total of 2730 participants) assessed the efficacy, safety

and acceptability of foods and supplements including high levels of phytoestrogens (i.e. red clover extracts, dietary soy, soy extracts, other types of phytoestrogens) for reducing hot flushes and night sweats in peri- or postmenopausal women.34 Seven trials used a red clover extract (in dosages ranging from 40 mg to 160 mg daily); five of these (including a total of 400 participants) were combined in a meta-analysis. No other trials had data suitable for inclusion in a meta-analysis.

The reviewers found no difference overall in the frequency of hot flushes between red clover extract and placebo (weighted mean difference –0.57, 95% CI –1.76 to 0.62). Of the remaining trials, two found a reduction in hot flushes with dietary soy (one versus placebo, one versus regular diet); five with soy extracts (versus placebo); and one with the isoflavone genistein (versus placebo) [49].

Red clover blossoms have been used for centuries in traditional herbal medicines. The majority of clinical trials do not support the efficacy of the red clover leaf extracts in alleviating hot flushes. While no serious adverse effects have been reported, there are concerns on the safety of using semi-purified isoflavones in women with a history of breast cancer.

It is generally recommended that women should eat phytoestrogen containing foods rather than taking supplements. Phytoestrogens are part of a healthy diet and may help lower blood cholesterol levels The optimal intake of dietary phytoestrogens appears to be around 50 mg day and a recent analysis has found that this intake level can reduce the frequency and severity of hot flushes As a rough guide, the phytoestrogen content of some foods are

250 ml soy milk – 15-60 mg
115 g block tofu – 13-43 mg
2 slices of soy and linseed bread – 7-15 mg
200 g tub of tofu yoghurt – 26 mg
1 tablespoon of soy grits – 25-32 mg

(ii) Black cohosh

Black cohosh (*Actaea racemosa*, formerly known as *Cimicifuga racemosa*) is a plant product prescribed to alleviate vasomotor symptoms. The mode of action is not known. Long term safety is not studied. Black cohosh, 40 mg orally daily and 0.6 mg orally daily were not superior to placebo. No significant difference at 60 days [50].

(iii) Evening primrose oil

Evening primrose oil is very popular among postmenopausal women. It is rich in gamma-linolenic and linolenic acid. Randomised placebo-controlled trial revealed that it is not effective to treat hot flushes [51].

(iv) Chinese herbs

Dong quai (*Angelica sinensis*) is a traditional Chinese medicine to treat hot flushes. Randomised trial did not prove to be better than placebo. Interactions with warfarin, increasing the risk of bleeding and photosensitisation have been reported.

(v) Ginseng

Ginseng is a perennial herb native to Korea and China. Studies have not proved Ginseng is superior to placebo. Side effects of postmenopausal bleeding and mastalgia had been reported. Interaction with warfarin is also noted.

(vi) St John's wort

St John's wort (*Hypericum perforatum*) has SSRI type effect. It relieves mild to moderate depression. The quality of the life of postmenopausal women had improved. However it is not effective in relieving vasomotor symptoms. When taken together it reduces the efficacy of cyclosporine, amitriptyline, warfarin and theophylline.

(vii) Agnus Castus (chasteberry)

Agnus Castus (*V. agnus-castus*) is claimed to reduce vasomotor symptoms. A combination of herbal products such as chaste tree, black cohosh, dong quai, red clover and American ginseng have found to reduce vasomotor symptoms.

(viii) Other herbs

Ginkgo biloba, hops, sage leaf, liquorice and valerian root are popular, but they were not proved to relieve vasomotor symptoms. Kava kava (*Piper methysticum*) was once popular to relieve anxiety and menopausal symptoms. This is banned in United kingdom due to the liver damage.

It must be kept in mind that just because they are marketed as natural products, they are not free of additives and toxic substances. A recent guideline from the National Institute for Health and Care Excellence (NICE) does not recommend the use of complementary therapies. Their efficacy has not been proved. No proper studies had been done. Long term safety is not assessed. Serious side effects like liver damage were reported. They may interact with some medications.

5.3 Vitamin E

Vitamin E 400 IU orally twice a day. Minimal decrease of 1 hot flash per day compared with placebo [52].

6. COMPLEMENTARY PROCEDURES

Acupuncture, reflexology, Ayurveda, osteopathy, hypnotherapy are popular among postmenopausal women.

(i) Acupuncture

There are difficulties with trial design particular in blinding to Sham acupuncture. In a recent meta-analysis acupuncture was no more effective than placebo for control of hot flushes.

In a recent meta-analysis in which six randomised sham-controlled trials were included in the final analysis, the authors failed to show beneficial effects of acupuncture over 'placebo' for control of menopausal hot flushes [53].

(ii) Reflexology

Reflexology targets to relieve or treat health conditions by application of pressure on specific points in the feet, hand and ears. In a randomised trial 67 women aged 45-60 years with vasomotor symptoms were randomised to traditional reflexology and foot massage. There was a reduction in vasomotor symptoms in both groups but no significant difference in both groups [54].

(iii) Homeopathy

Homeopathy is a mechanism of biological response to ultra molecular dilution. Many claim that this scientifically unclear. More researches and larger randomized clinical trials are required to find the benefits.

(iv) Magnetism

It is not uncommon to see many women in postmenopausal women wear magnetic therapy bracelets and insoles as. Magnetic therapy cannot reduce hot flushes and no evidence of benefits at present.

7. DIET AND SUPPLEMENTS

7.1 Vitamins and Minerals

Various supplements containing Vitamins, such as E and C, and minerals, such as selenium, are popular among postmenopausal women. It is not proven to improve vasomotor symptoms.

7.2 Vitamin E

In one study, Vitamin E 800 i.u daily was found to have statistically significant improvement of hot flushes in breast cancer patients compared to placebo. In another study garbapentin was found to be superior to Vitamin E in reducing vasomotor symptoms.

7.3 Stellate Ganglion Blockade

Stellate ganglion blockade is injection of local anaesthetics into the stellate ganglion. This is effective in relieving hot flushes. Preliminary studies are promising.

Women with postmenopausal symptoms require relieve of their symptoms. Some of them may not keen to use the oestrogen treatment or have contraindications to use the hormones. They should be offered with some alternate options. We should be able to discuss the efficacy and benefits on evidence based knowledge.

7.4 Role of Oestrogen Therapy

The natural onset of menopause occurs between the ages of 45–55 years [55]. HRT reduce risk of cardiovascular diseases e.g., by altering the lipid profile.16 and reducing serum uric acid level [56].

Single intranasal administration of 17-β-estradiol in healthy postmenopausal women had increased cerebral perfusion. In a study sixteen healthy postmenopausal women with the mean age of 54±3 years were given 300 μg of intranasal 17-β-estradiol. Their heart rate, systolic/diastolic blood pressure, peak systolic velocity, end-diastolic velocity, and velocity-time integral (VTI) at the level of internal carotid and

posterior tibial arteries were studied before and after 30, 60, and 180 minutes of drug administration. The internal carotid artery VTI showed statistically significant (P < .05) variations at all the time intervals after administration of the drug (30, 60, and 180 minutes) when compared with "time zero. The systolic/diastolic blood pressure and heart rate did not significantly differ before and after drug administration. No significant variation was found at the posterior tibial artery. However further studies are required to analyse the peripheral blood flow [57].

Single dose of intranasal 17-beta-estradiol to healthy postmenopausal women was found to increase ophthalmic artery perfusion. Twenty-one healthy women in natural menopause for at least 6 months (mean age: 53.2±2.9 years) received 300 µg intranasal 17-beta-estradiol. The heart rate, systolic and diastolic blood pressure, ophthalmic artery velocity at systolic and diastolic peak and its flow curve integral (FCI) before and 30, 60 and 180 minutes after the administration of the drug were evaluated. The ophthalmic artery FCI showed statistically significant variations ($p<0.001$) of velocity (cm/sec) compared to T0 (speed recorded at baseline before drug administration). Moreover, systolic blood pressure, diastolic blood pressure and heart rate did not significantly differ each other after drug administration [58]

8. CONCLUSION

Postmenopausal women suffer from vasomotor symptoms, psychological disturbances, atrophy of vagina and lack of sexual desire. HRT is effective in relieving postmenopausal symptoms. Transdermal route which may theoretically reduce the risk of thrombo embolic disease due to hepatic by pass. Transvaginal estrogen may be considered to provide topical effects with less systemic absorption. Unopposed estrogen should not be used in women with an intact uterus due to endometrial cancer risk.

If they do not wish to take oestrogen, they should be offered an alternative. Lifestyle modification is important. The merits of medications and other options are discussed. Antidepressants are effective in reducing the vasomotor symptoms. Venlafaxine is widely prescribed. clonidine and megestrol can reduce the vasomotor symptoms. Gabapentin also can reduce the vasomotor symptoms. Data on Data on most nutritional supplements are limited by the lack of placebo-controlled trials and by existing trials that have generally shown no differences in results between such therapy and placebo.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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