Sci

MDPI

Review

Hormone Replacement Therapy (HRT) Shortages for Treating Menopause: What Can Clinicians Do to Relieve Symptoms and Concerns?

Tomas Fait [1,2,*] and Michal Vrablik [3]

[1] Department of Obstetrics and Gynecology, 2nd Faculty of Medicine, Charles University Prague, 153 00 Prague, Czech Republic
[2] Department of Health Studies, Faculty of Polytechnics Jihlava, 586 01 Jihlava, Czech Republic
[3] Department of Internal Medicine, 1st Faculty of Medicine, Charles University Prague, 128 00 Prague, Czech Republic; michal.vrablik@vfn.cz
* Correspondence: tomas.fait@lf2.cuni.cz; Tel.: +420-603-910-473

Abstract: Hormone replacement therapy (HRT) is a treatment for acute climacteric syndrome, with the best effectivity. It also prevents bone loss and fractures. Ischemic heart disease prevention and cognitive function improvement have been observed with HRT, only when started early (critical window hypothesis). There is a large scale of complementary and alternative medicines for women in preference to non-hormonal treatment. Unfortunately, they do not always accompany reliable documentation of efficacy and safety from well-performed studies.

Keywords: hormone replacement therapy; critical window hypothesis; tibolone; phytoSERMs; TSEC; DT56a; pollen extract; antidepressants; fezolinetant

Citation: Fait, T.; Vrablik, M. Hormone Replacement Therapy (HRT) Shortages for Treating Menopause: What Can Clinicians Do to Relieve Symptoms and Concerns? *Sci* **2024**, *6*, 46. https://doi.org/10.3390/sci6030046

Academic Editor: Michele Roccella

Received: 4 June 2024
Revised: 27 July 2024
Accepted: 31 July 2024
Published: 2 August 2024

1. Introduction

Hormone replacement therapy (HRT, menopause hormone therapy, MHT) is the most effective treatment for vasomotor problems of acute climacteric syndrome, genitourinary syndrome, and has been proven to prevent bone loss and fractures. The data are strongly in support of the conclusions of the latest NAMS recommendation from 2022 [1].

In women younger than 60, or within 10 years of the onset of menopause without known contraindications to HRT, its benefits outweigh the risks both in the treatment of vasomotor symptoms and in the prevention of bone loss. Later initiation of the treatment is no longer recommended due to a higher risk of ischemic heart disease, stroke, thromboembolic disease, and dementia [2].

Long-term use is reserved for women with persistent vasomotor syndrome and women with primary ovarian insufficiency (premature ovarian failure). In women with genitourinary syndrome without an indication for systemic HRT, who are not helped by over-the-counter preparations, low-dose vaginal estrogen treatment, vaginal dehydroepiandrosterone, or oral ospemifene are recommended [3].

The risks of hormonal treatment vary according to the type, dose, duration of use, route of administration, time of initiation, and progestin used. Treatment should be individualized with regular re-evaluations of the benefits and risks [4].

It is more appropriate to use incidence increases rather than relative risk values to discuss the risks of HRT. There is a group of women for whom HRT is contraindicated and a group for whom concerns prevail even after education. For those, we need an alternative treatment with proven effectiveness and safety.

2. Methodology

This article is not a systematic review or re-analysis of studies. It is a narrative review. We have summarized today's decision making in the daily practice of climacteric medicine.

Sources of scientific support were found in PubMed and Medline databases, laying emphasis on the newest recommendations of the International Menopause Society and the North American Menopause Society. We used findings from the period of 2020 until 2023 and the following key words: HRT, MHT, quality of life, breast cancer, thromboembolic disease, TSECs, vulvovaginal atrophy, tibolone, fezolinetant, phytoestrogen, antidepressants, TCM. The main aim of this article is to demonstrate the importance and possibilities of estrogen deficiency syndrome therapy.

3. It Is Not Just about the Quality of Life

The symptomatology of acute climacteric syndrome is dominated by hot flushes followed by sweating. According to the SWAN study (Study of Women's Health Across the Nation), there are two syndromes—vasomotor and psychosomatic. Organic (subacute)—skin, urogenital, and body weight changes—and metabolic (chronic)—lipid spectrum, osteoporosis—effects can already lead to health damage. They are also referred to as estrogen-deficient metabolic syndrome [5].

It is generally agreed that vegetative symptoms reduce the quality of life, but do not threaten a woman's health. However, recent studies show that these symptoms are a significant risk factor for a woman's cardiovascular system [6].

Hot flushes are observed by 70% of women in perimenopause, by only 30% of women around the age of sixty, and only 9% after the age of seventy. They last an average of 7.4 years. They start with a feeling of heat or burning and spread from the head area caudally, followed by an attack of sweating, sometimes accompanied by headaches or palpitations. On average, they last 3–4 min with a range from a few seconds to 60 min. There are significant cross-cultural and inter-individual differences in the rate of hot flushes, influenced by lifestyle, genetic makeup, being overweight, or smoking. Untreated hot flushes affect quality of life, disrupt sleep, and negatively affect mood, but are also risk factors for hypertension and endothelial dysfunction [7].

In a group of more than 11,000 women followed for 14 years, a double risk of ischemic heart disease was demonstrated in women with hot flashes. The causative mechanism is the connection of hot flushes with higher blood pressure, a change in the lipid spectrum, an increase in insulin resistance, and inflammatory markers [8]. Upon MRI of the brain, women with hot flashes have been found to have a greater number of hyperdense foci in the white matter, which are associated with a threefold risk of stroke and a twofold risk of dementia [9].

4. Hormonal Therapy

As with any medicine, indications and contraindications of HRT must be followed (Tables 1 and 2) [10,11]. Current guidelines for HRT use recommend starting treatment at the lowest effective dose [12].

Table 1. Indication of HRT.

Acute climacteric syndrome	vegetative symptoms	
	mood changes	
Estrogen-deficiency syndrome	organic	urogenital atrophy
	metabolic	prevention of osteoporosis
		primary prevention of ischemic heart disease

Preparations containing a low dose, even ultra-low dose, are demonstrably effective in the treatment of acute climacteric syndrome in postmenopausal women [13,14] and in the prevention of postmenopausal osteoporosis [15].

Low doses are more neutral to some of the side effects of HRT, especially the increase in mammographic density [16] and the occurrence of irregular bleeding [17,18].

HRT improves mood and has a beneficial effect on depression associated with menopause. Cognitive function improvement has been observed with HRT only when started early (critical window hypothesis, healthy cell bias hypothesis). At the age of over sixty-five, on the other hand, the risk of dementia increases with HRT. The same relationship applies to Alzheimer's disease [19] and ischemic heart disease [20,21].

Table 2. Contraindication of HRT.

breast cancer—active, personal history, suspection
estrogen-dependent malignancy and suspection on it - unclear vaginal bleeding - endometrial stromal sarcoma - meningeoma - stomach cancer with estrogen receptors - urinary bladder cancer with estrogen receptors
thromboembolic disease (acute or personal history)
ischaemic heart disesase (acute or personal history)
active hepatopathy
alergy for components of drug

The risk of breast cancer depends on the dose of estrogen, the progestin used, and the duration of HRT use. Even here, however, we do not find a reason for the attributive termination of HRT administration in women at 65 years of age. The increased risk of breast cancer with the long-term use of combined hormone replacement therapy is ridiculously small. Nevertheless, it is still one of the most important reasons for the rejection of HRT by doctors and laypeople, which is demonstrably harmful to a woman's health [22].

From the point of view of the risk of breast cancer and thromboembolic disease, micronized progesterone and dydrogesterone appear to be more neutral than other progestogens [23,24].

The Role of HRT in the Management of Osteoporosis

The preventive and therapeutic effects of HRT have been documented in numerous studies from the last century, when these were considered one of the most important effects for the treatment of acute climacteric syndrome and were also considered a separate indication for its administration. Paradoxically, the Women's Health Initiative study, which led to a significant shift away from HRT, was the most extensive study confirming its beneficial effects on bone health. For the combination of conjugated equine estrogens (CEEs) + medroxyprogesterone acetate (MPA), it showed a 24% reduction in osteoporotic fractures (HR 0.76, 95% CI 0.69–0.83), which is significant even after adjustment to age, body mass index, history of falls or bone mineral density (BMD) [25], as well as a synergistic effect of HRT and vitamin D intake with calcium, where there is a reduction in the risk of fractures to HR of 0.59 (95% CI 0.38–0.93). A 2001 meta-analysis of twenty-two placebo-controlled trials showed a reduction in nonvertebral fractures with an RR of 0.73 (95% CI 0.56–0.94) after at least 12 months of HRT use, with greater significance in women who started before age 60 regardless of baseline BMD [26]. Also, a 2016 meta-analysis of twenty-eight randomized placebo-controlled trials confirmed these data with an RR for all fractures of 0.74 (95% CI 0.69–0.80), femoral neck fractures with an RR of 0.72 (95% CI 0.53–0.98), and vertebral fractures with an RR of 0.63 (95%CI 0.44–0.91) [27].

Both standard and low-dose estrogens prevent bone loss by inhibiting osteoclast activity and reducing bone turnover, reducing the number of osteoporotic fractures in all locations, even in women without osteoporosis. In addition to appropriate HRT, management also includes supplementation with calcium, vitamin D, and exercise. However, the continuation or discontinuation of HRT is governed by its extra-bone effects [28].

5. TSECs

A new direction in climacteric medicine is the group of TSECs (tissue-selective estrogen complexes). It is a combination of SERM (selective estrogen receptor modulator) with estrogen to achieve the ideal combination of osteoporosis prevention and treatment of acute climacteric syndrome.

The combination of bazedoxifene (BZA) with conjugated equine estrogens (CEEs) was investigated. Combinations of 0.625 mg or 0.45 mg CEE with 20 mg or 40 mg BZA are considered to be promising. Efficacy for acute climacteric syndrome and prevention of osteoporosis with safety comparable to a placebo for the breast and endometrium has been demonstrated in a three-year study of 3397 women aged 40–75, with a uterus in situ [29,30].

The effect of BZA/CEE at a daily dose of 20 mg/0.45 mg or 20 mg/0.625 mg, 20 mg BZA, and placebo on sexual function and quality of life was monitored in a group of 652 postmenopausal women with vaginal atrophy after 12 weeks of application. Both combinations of TSECs significantly ($p < 0.05$) improved lubrication scores (assessed by ASEX) versus placebo and BZA alone. Similarly, the quality of life (assessed by MENQOL) was significantly ($p < 0.05$) increased in vasomotor symptoms, sexual functions, and in the total score compared to placebo and BZA alone [31].

6. Vulvovaginal Atrophy (Genitourinary Menopausal Syndrome)

An integral part of climacteric syndrome is also genitourinary menopausal syndrome—GSM (vulvovaginal atrophy, vaginal dryness, burning and irritation, pain during intercourse and reduced lubrication, urgent incontinence, dysuria, and repeated urinary tract infections). Here, too, hormone therapy is the best solution so far. Low-dose vaginal preparations are effective and safe due to minimal systemic effects. In cooperation with an oncologist, they can also be used in patients with a history of breast cancer undergoing therapy with tamoxifen or aromatase inhibitors. An opposition of local estrogens by progestins is not necessary [32].

The drug of choice is vaginally applied estradiol or estriol.

In a one-year study, 205 women were treated with ten micrograms of estradiol twice a week, and 104 women were given a placebo. Women were older than 45 years, at least 2 years postmenopausal (FSH > 40 mIU/mL, estradiol < 20 pg/mL), and had at least 3 of 6 subjective symptoms of vaginal atrophy (vaginal dryness, burning, pain, dysuria, dyspareunia, bleeding after intercourse). At the beginning of treatment, they had $\leq$5% surface cells in vaginal cytology, and the ultrasound thickness of the endometrium did not exceed 4 mm. Of the objective marks, the graduation index was monitored, which improved significantly from the end of the second week of treatment, and the improvement lasted even after 52 weeks of follow-up. In the treated group, the number of surface cells increased to 13% ($p < 0.001$), and the vaginal pH decreased significantly. Based on the macroscopic image of the vaginal mucosa, the researchers were able to determine which woman was using effective treatment from the end of the second week. A subjective improvement in symptoms of vaginal atrophy occurred from the 4th week of treatment, and a statistically significant improvement ($p = 0.003$) was achieved at the 8th week of treatment [33].

In a safety study of endometrial response to treatment, 336 women were followed. After one year of follow-up, endometrial polypus was found in 0.7% of cases and weak endometrial proliferation in 0.3%. Ultrasound endometrial thickness did not change in the treatment group (2.04 mm at baseline, 1.94 mm after one year of treatment) [34]. Thus, with a total dose of 1.14 mg of estradiol per year, symptoms of GSM can be safely and effectively treated.

An alternative can be ospemifene, which acts on the vaginal mucosa as an estrogen agonist. It has a beneficial effect on bone and the lipid spectrum, a neutral effect on the endometrium, and an anti-estrogenic effect on breast tissue. A third-phase pilot study enrolled 826 postmenopausal women suffering from vulvovaginal atrophy. Inclusion criteria included <5% surface cells in vaginal smear, vaginal pH > 5, and at least one

bothersome symptom (vaginal dryness, burning, dysuria, bleeding, dyspareunia). The placebo was compared with 30 and 60 mg of ospemifene for 12 weeks. Tolerance was comparable in all groups, laboratory parameters did not change, and no endometrial hyperplasia was detected. Improvement in symptoms (dyspareunia, vaginal dryness) was statistically significant for the 60 mg dose [35].

While the production of estradiol in the ovaries practically ceases with menopause, the production of dehydroepiandrosterone (DHEA, prasterone) in the adrenal glands decreases by 50% and then slowly declines. Thanks to the conversion in the target tissues, DHEA then becomes the only source of estrogens and androgens for the postmenopausal organism. Their formation and degradation are mainly intracellular in the target tissue. The decrease in DHEA is associated with a decrease in local estrogen production in the cells of the vagina and leads to the development of vulvovaginal atrophy, which affects half of postmenopausal women aged 50–60, and even three-quarters of postmenopausal women in their 70s, which can be explained more by a decrease in DHEA than just a decrease in levels estradiol alone. In the treatment of moderate and severe dyspareunia based on postmenopausal urogenital atrophy, a preparation with 6.5 mg of prasterone in a vaginal tablet with daily application has recently been registered. Local productions of estrogen and testosterone without changes in systemic levels is typical only for a minimal dose vaginally applied daily [36].

7. Tibolone

Tibolone is the only therapeutic approach to climacteric symptoms, prevention of osteoporosis, and urogenital atrophy with the same efficacy as hormone replacement therapy. Tibolone has more positive effects on sexuality and mood changes in menopausal women. It decreases the mammographic density. Its safety for breast cancer is the same as for estrogen therapy only and is better than for estrogen/gestagen therapy. Tibolone is the first choice for postmenopausal women with mood and sexuality disorders, women with mastodynia, and high mammographic density [37].

8. From Phytoestrogens to phytoSERMs (Selective Estrogen Receptor Modulators)

Phytoestrogens are non-steroidal plant components capable of producing an estrogenic effect. They are usually divided into isoflavones (daidzein, genistein, biochanin A, formononetin, glycitein...), lignans (secoisolariciresinol diglucoside, matairesinol—precursors of mammalian lignans enterodiol and enterolactone) and coumestans [38].

Isoflavones have a significantly higher (fivefold) affinity for estrogen receptor beta than for the alpha receptor. Phytoestrogens have about 10,000 times less estrogenic effect than estradiol. This is the basis for their higher safety, but also lower effect compared to HRT. In addition to selective estrogenic effects, they can reduce free radicals with a theoretical cancer-protective effect through the mechanism of inhibition of tyrosine kinases [39].

The reduction in the frequency and intensity of hot flashes as the main symptom of acute climacteric syndrome is most often around 30–35% when using phytoestrogens. The placebo effect is 25–30%. On the other hand, some studies show an effect greater than 70% [40]. There are well-designed studies showing a protective effect on bone tissue [41] with a standardized soybean sprout extract with a dose-related effect, as well as studies with similar amounts of soy isoflavones with no demonstrable effect [42].

The metabolism of isoflavones could explain why the effect fluctuates even with properly manufactured preparations. The main soy isoflavones beta-D-glycosides genistin and daidzein are hydrolyzed by bacterial beta-glucosidases in the small intestine to genistein and daidzein, which are absorbed into the body. Daidzein is further metabolized to equol and O-demethylangolensine. Genistein is metabolized to p-ethylphenol and 4hydroxyphenyl-2-propionic acid. The ability to produce equol, given by an individual's genetic make-up and the composition of their intestinal flora, may be the basis for explaining the fluctuating efficacy of isoflavones in insufficiently large studies [43–45]. If the manufacturer does not use standardized extracts, it can have a significant effect on the

composition and source of phytoestrogens. The content of phytoestrogens in soy, but also in red clover, varies depending on the place of cultivation.

DT56a is an extract from fermented soybeans, and it contains eleven different components from the phytoestrogen group. Thanks to their synergistic effect, it works as a SERM (selective estrogen receptor modulator)—it has an estrogenic effect in cerebrovascular and bone tissue, but not in the uterus and breast [46]. The binding of DT56a to estrogen receptor beta is 100,000 times higher than to the alpha receptor. DT56a also inhibits enzyme activity and has antioxidant effects [47].

In a Greek one-year prospective study, 89 postmenopausal women with acute climacteric syndrome were randomized to 644 mg DT56a daily (27 women) and low-dose HRT 1 mg estradiol + 0.5 mg norethisterone acetate (26 women), and controls (36 women) who remained untreated. Both DT56 and HRT were associated with a significant ($p < 0.001$) reduction in the Kupperman index (−3.98 versus −5.06) versus no treatment (+1.76). Untreated women showed a significant decrease in BMD in the lumbar spine according to the T-score (−0.6 . . . −0.85, p = 0.001), which did not change in the treated women. There was no change in bone density in the neck of the femur, mammographic findings, or in the thickness of the endometrium in any of the groups. There were no changes in the lipid profile either [48].

In a Spanish study, 631 women with acute climacteric symptoms were given DT56a for 4 weeks. After 2 and 4 weeks, there was a significant reduction in the number of hot flashes in 80.7% and in their strength in 36% [49], which was replicated in a study with the same design performed in the Czech Republic [50].

9. Pollen Extracts

One method of alternative therapy for climacteric syndrome is the use of pollen extracts. The extraction of active substances requires a special technology, which only obtains the content of the pollen grains without the proteins of their outer layers, which could cause allergies. These are referred to as PCP (purified cytoplasm of pollen). While bee products containing whole pollen grains and a variable mixture of pollen from different plants are sometimes used, the patented PI82/GC Fem pollen extract is extracted from well-defined monocultures with an emphasis on the time of collection. It inhibits the reuptake of serotonin in the hypothalamus, similarly to SSRIs, thereby affecting sleep and thermoregulation. However, unlike SSRIs, it does not affect the enzymes involved in the metabolism of tamoxifen [51–53].

In an open-label, multicenter, placebo-controlled study, 417 postmenopausal women were administered two tablets of the extract at a dose of 160 mg per day. Already after 3 months, significant decreases in hot flashes by 65% ($p = 0.0659$) in frequency and 64% in intensity ($p = 0.0003$), sweating by 67% or 66% ($p < 0.0001$), irritability by 54% ($p < 0.0001$), and fatigue by 51% ($p < 0.0001$) were observed [54].

10. Antidepressants

To understand the mechanism of hot flushes, it is important to know that there are no differences in estradiol levels in the plasma, urine, or tissues of symptomatic and asymptomatic women; however, symptomatic women have higher levels of the noradrenaline metabolite MHPG (3-methoxy 4-hydroxyphenylglycol) and increased heart rhythm variability. Symptomatic women have a narrowed thermoneutral zone in the thermoregulatory center in the preoptic area of the hypothalamus. Dysregulation can be caused by age and health conditions (multiple sclerosis, thyroid disorder, brain and spinal cord injury).

Expansion of the thermoneutral zone can be achieved by administering estrogen, clonidine, or drugs that increase tryptophan or serotonin levels. Estrogens affect the serotonergic system—they increase serotonin synthesis, reduce its breakdown, and modulate its receptors. In the noradrenergic system, estrogens increase the production of noradrenaline, increasing its availability and slowing its breakdown [55].

In the review of studies of non-hormonal treatment SSRIs (selective serotonin reuptake inhibitors)—paroxetine, fluoxetine, sertraline, citalopram, and escitalopram influenced acute climacteric syndrome in 28–55%.

The SNRIs (selective serotonin-norepinephrine reuptake inhibitors) venlafaxine and desvenlafaxine impacted on the same outcomes by 35–58% and 55–68%, respectively.

Desvenlafaxine is the only molecule documented by studies meeting the FDA's criteria to initiate efficacy validation. It has been studied in a total of more than 4200 women. At a dose of 100 mg, it achieved a significant ($p < 0.001$) reduction in the number and intensity of hot flushes and episodes of night awakening after 4 and 12 weeks of use. In a one-year study with 315 women, the only adverse effect was an increased number of nauseas, especially in the first week of use, which could be reduced by halving the dose of desvenlafaxine (3 days 50 mg, 1 day 100 mg) [56].

Thus, when treating depression, we can also treat hot flashes at the same time and vice versa.

11. Selective Antagonists of Neurokinine-3 Receptors

In mammals, four tachykinins are described: substance P, neurokinin A, neurokinin B, and edokinin/hemokinin. Tachykinins are group of polyfunctional neuropeptides. Tachykinins are joined to the pathophysiology of pain, inflammation, and neurodegeneration through receptors NK 1, NK2, and NK3. Fezolinetant is the first selective oral antagonist of the neurokinin-3 receptor.

Fezolinetant works by blocking neurokinin B binding on the kisspeptin/neurokinin/dynorphin (KNDy) neuron to modulate neuronal activity in the brain's temperature control center (the hypothalamus) to reduce the number and intensity of hot flashes and night sweats.

One study describes the high efficacy of fezolinetant 45 mg daily in the treatment of moderate-to-severe vasomotor symptoms associated with menopause. Fezolinetant may cause early transient liver function test elevations greater than three times the upper limit of normal in about 2% of patients [57]. The non-hormonal characteristic of this therapy is promising for patients with contraindication to hormone replacement therapy, especially for breast cancer survivors.

12. Traditional Chinese Medicine

Traditional Chinese medicine (TCM) is based on completely different principles than Western medicine. It is based on the theory that qi energy consists of two opposite but mutually present components, yin and yang. According to TCM, hot flushes are caused by a disturbance in the flow of qi energy in the kidney pathway.

In a double-blind, randomized trial of 147 women, of whom 123 completed the trial, Heyan Kuntai capsules were compared with estradiol valerate. After three months, both drugs reduced the rate of climacteric syndrome in 92%, and without difference in effect in 96.5% [58].

A placebo-controlled study of Zhibai Dihuang showed a significant improvement in climacteric syndrome after 12 weeks of treatment in a group of thirty-one women [59]. The rapid onset of effect with acupuncture is remarkable, where symptoms improved within 24 h in 62% of those treated versus 27% in the control group [60]. In contrast, a re-analysis of six placebo-controlled studies published up to 2008 did not show a significant effect of acupuncture on hot flashes [61]. The analysis conducted in seventeen databases found 106 articles, of which twenty-three were excluded for the target group of women after breast cancer, six for comparison with pharmacotherapy, and the rest for lack of a control. Most of them reported a good effectiveness of acupuncture.

The re-analysis searched for published randomized trials in English only between 2004 and 2011. Eleven trials [62] were eligible. Out of eight acupuncture studies, five showed a significant effect of acupuncture on hot flushes, one of them simultaneously showed improvement in sleep and pain, and two showed improvements in psychological

parameters. All three studies of phytotherapy showed a significant effect on hot flashes, one of them also on psychological parameters, another on pain, and the last one on sleep and pain. One study used moxibustion and found a significant reduction in hot flashes, improved mood, and reduced pain. None of the studies reported adverse effects.

The results of studies dealing with the use of classical Chinese medicine in the treatment of climacteric syndrome are encouraging; however, the difficulty of applying acupuncture excludes this method from our daily clinical practice. Studies on traditional Chinese herbal medicine also show a beneficial effect. However, different mixtures are being studied, so it is difficult to draw clear clinical recommendations from the published studies. The TCM philosophy itself does not work with the flat application of one herbal mixture or standard stimulation of the same acupuncture points.

13. Healthy Lifestyle

Physical activity alleviates the symptoms of acute climacteric syndrome. In a recent meta-analysis of 21 randomized controlled trials with 2884 participants, exercise significantly reduced the severity of vasomotor symptoms (10 studies, standardized mean difference [SMD] = 0.25; 95% confidence interval [CI]: 0.04 to 0.47, $p = 0.02$), but surprisingly not their frequency (SMD = 0.14, 95% CI: −0.03 to 0.31, $p = 0.12$) [63].

At the same time, it is also suitable for maintaining muscle strength and optimal bone microarchitecture in the prevention of fractures [64].

14. Conclusions

Vegetative symptoms of menopause reduce the quality of life. Recent studies show that these symptoms are a significant risk factor in a woman's cardiovascular system. Hormone replacement therapy is the best therapy for these symptoms. In the case of an early start, HRT can prevent bone loss, atherosclerosis, and dementia. The safety of HRT depends on timing, doses, application way, and composition (especially the type of progestogens). Tibolone is the only therapeutic approach to alleviate climacteric symptoms, prevent osteoporosis, and manage urogenital atrophy with the same efficacy as HRT.

An extensive range of complementary and alternative medicines are promoted for the therapy of acute climacteric syndrome. Scientific studies are not always available. Physical activity, antidepressants, pollen extracts of some phytoestrogens, and fezolinetant show promising evidence of safety and efficacy.

Author Contributions: Conceptualization T.F. and M.V.; methodology T.F.; validation T.F. and M.V.; formal analysis T.F.; investigation T.F.; data curation T.F.; writing—original draft preparation T.F.; writing—review and editing M.V.; visualization T.F. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Data Availability Statement: No new data were created.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. NAMS Position Statement. The 2022 Hormone Therapy Position Statement. *Menopause* **2022**, *29*, 767–794. [CrossRef] [PubMed]
2. Salpeter, S.R.; Cheng, J.; Thabane, L.; Buckley, N.S.; Salpeter, E.E. Bayesian metaanalysis of hormone therapy and mortality in younger postmenopausal women. *Am. J. Med.* **2009**, *122*, 1016.e1–1022.e1. [CrossRef] [PubMed]
3. Fait, T. Menopause hormone therapy: Latest developments and clinical practice. *Drugs Context* **2019**, *8*, 212551. [CrossRef] [PubMed]
4. Santoro, N.; Epperson, C.N.; Mathews, S.B. Menopausal symptoms and their management. *Endocrinol. Metab. Clin. N. Am.* **2015**, *44*, 497–515. [CrossRef] [PubMed]
5. Avis, N.E.; Crawford, S.L.; Greendale, G.; Bromberger, J.T.; Everson-Rose, S.A.; Gold, E.B.; Hess, R.; Joffe, H.; Kravitz, H.M.; Tepper, P.G.; et al. Duration of menopause vasomotor symptomps over the menopause transition. *JAMA Intern. Med.* **2015**, *175*, 531–539. [CrossRef]

6. Biglia, N.; Cagnacci, A.; Gambacciani, M.; Lello, S.; Maffei, S.; Nappi, R.E. Vasomotor symptoms in menopause: A biomarker of cardiovascular disease risk and other chronic diseases? *Climacteric* **2017**, *20*, 306–312. [CrossRef] [PubMed]
7. Thurston, R.; Chang, Y.; Barinas-Mitchel, E.; Jennings, J.R.; von Känel, R.; Landsittel, D.P.; Matthews, K.A. Physiologically assessed hot flashes and endothelial function among midlife women. *Menopause* **2017**, *24*, 886–893. [CrossRef]
8. Herber-Gast, B.; Brown, W.J.; Mishra, G.D. Hot flushes and night sweats are associated with coronary heart disease risk in midlife: A longitudinal study. *BJOG* **2015**, *122*, 1560–1567. [CrossRef]
9. Thurston, R.C.; Aizenstein, H.J.; Derby, C.A.; Sejdić, E.; Maki, P.M. Menopausal hot flashes and white matter hyperintensities. *Menopause* **2016**, *23*, 27–32. [CrossRef]
10. Mendoza, N.; Ramírez, I.; de la Viuda, E.; Coronado, P.; Baquedano, L.; Llaneza, P.; Nieto, V.; Otero, B.; Sánchez-Méndez, S.; de Frutos, V.; et al. Eligibility criteria for Menopausal Hormone Therapy (MHT): A position statement from a consortium of scientific societies for the use of MHT in women with medical conditions. MHT Eligibility Criteria Group. *Maturitas* **2022**, *166*, 65–85. [CrossRef]
11. Davis, S.R.; Taylor, S.; Hemachandra, C.; Magraith, K.; Ebeling, P.R.; Jane, F.; Islam, R.M. The 2023 Practitioner's Toolkit for Managing Menopause. *Climacteric* **2023**, *26*, 517–536. [CrossRef] [PubMed]
12. Notelovitz, M.; Lenihan, J.P.; McDermont, M.; Kerber, I.J.; Nanavati, N.; Arce, J.-C. Initial 17estradiol dose for treating vasomotor symptoms. *Obstet. Gynekol.* **2000**, *95*, 726–731. [CrossRef]
13. Panay, N.; Ylikorkala, O.; Archer, D.F.; Gut, R.; Lang, E. Ultra-low-dose estradiol and norethisterone acetate: Effective menopausal symptom relief. *Climacteric* **2007**, *10*, 120–131. [CrossRef] [PubMed]
14. Stevenson, J.C.; Durand, G.; Kahler, E.; Pertynski, T. Oral ultra-low dose continuous combined hormone replacement therapy with 0.5 mg 17-estradiol and 2.5 mg dydrogesterone for the treatment of vasomotor symptoms: Results from a double-blind, controlled study. *Maturitas* **2010**, *67*, 227–232. [CrossRef] [PubMed]
15. Gambacciani, M.; Cappagli, B.; Ciaponi, M.; Pepe, A.; Vacca, F.; Genazzani, A.R. Ultra low-dose hormone replacement therapy and bone protection in postmenopausal women. *Maturitas* **2008**, *59*, 2–6. [CrossRef] [PubMed]
16. Lundström, F.; Bydgeson, M.; Svane, G.; Azavedo, E.; von Schoultz, B. Neutral effect of ultra-low-dose continuous combined estradiol and norethisterone acetate on mammographic breast density. *Climacteric* **2007**, *10*, 249–256. [CrossRef]
17. Sturdee, D.W.; Archer, D.F.; Rakov, V.; Lang, E. Ultra-low-dose continuous combined estradiol and norethisterone acetate: Improved bleeding profile in postmenopausal women. *Climacteric* **2008**, *11*, 63–73. [CrossRef]
18. Bergeron, C.; Nogales, F.F.; Rechberger, T.; Tatarchjuk, T.; Zipfel, L. Ultra low dose continuous combined hormone replacement therapy with 0.5mg 17beta-oestradiol and 2.5mg dydrogesterone: Protection of the endometrium and amenorrhoea rate. *Maturitas* **2010**, *66*, 201–257. [CrossRef]
19. Koire, A.; Joffe, H.; Buckley, R. Menopausal Hormone Therapy and the Mind: The Role of Hormone Replacement in the Prevention and Treatment of Cognitive Decline, Dementia, and Cognitive Dysfunction of Depression. *Harv. Rev. Psychiatry* **2022**, *30*, 215–225. [CrossRef]
20. Kim, J.; Chang, J.H.; Jeong, M.J.; Choi, J.; Park, J.; Baek, C.; Shin, A.; Park, S.M.; Kang, D.; Choi, J.Y. A systematic review and metaanalysis of effects of menopause hormone therapy on cardiovascular diseases. *Sci. Rep.* **2020**, *10*, 20631. [CrossRef]
21. Fait, T.; Vrablik, M. Coronary heart disease and hormone replacement therapy—From primary and secondary prevention to the window of opportunity. *Neuro Endocrinol. Lett.* **2012**, *33* (Suppl. S2), 17–21. [PubMed]
22. Tan, D.A.; Dayu, A.R.B. Menopausal hormone therapy: Why we should no longer be afraid of the breast cancer risk. *Climacteric* **2022**, *25*, 362–368. [CrossRef] [PubMed]
23. Ruan, X.; Mueck, A.O. Primary choice of estrogen and progesteron as components of HRT. *Climacteric* **2022**, *25*, 443–452. [CrossRef] [PubMed]
24. Fournier, A.; Berino, F.; Clavel-Chapelon, F. Unequal risks for breast cancer associated with different hormone replacement therapies: Results from the E3N cohort study. *Breast Cancer Res. Treat.* **2008**, *107*, 103–111. [CrossRef] [PubMed]
25. Cauley, J.A.; Robbins, J.; Chen, Z.; Cummings, S.R.; Jackson, R.D.; LaCroix, A.Z.; LeBoff, M.; Lewis, C.E.; McGowan, J.; Neuner, J.; et al. Effects of estrogen plus progestin on risk of fracture and bone mineral density: The Women's Health Initiative randomized trial. *JAMA* **2003**, *290*, 1729–1738. [CrossRef] [PubMed]
26. Robbins, J.A.; Argaki, A.; Crandall, C.J.; Manson, J.E.M.; Carbone, L.; Jackson, R.; Lewis, C.E.C.; Johnson, K.C.; Sarto, G.; Stefanick, M.L.; et al. Women's Health Initiative clinical trials: Interaction of calcium and vitamin D with hormone therapy. *Menopause* **2014**, *21*, 116–123. [CrossRef] [PubMed]
27. Torgerson, D.J.; Bell-Syer, S.E.M. Hormone replacement therapy and prevention of nonvertebral fracture: A meta-analysis of randomized trials. *JAMA* **2001**, *285*, 2891–2897. [CrossRef] [PubMed]
28. Zhu, L.; Jiang, X.; Sun, Y.; Shu, W. Effect of hormone therapy on the risk of bone fractures: A systematic review and meta-analysis of randomized controlled trials. *Menopause* **2016**, *23*, 461–470. [CrossRef] [PubMed]
29. Lobo, R.A.; Pinkerton, J.V.; Gass, M.L.; Dorin, M.H.; Ronkin, S.; Pickar, J.H.; Constantine, G. Evaluation of BZD/CEE for treatment of menopausa symptoms and effects on metabolic parameters and overall safety profile. *Fertil. Steril.* **2009**, *92*, 1025–1038. [CrossRef]
30. Pickar, J.H.; Yeh, I.T.; Bachmann, G.; Sperrof, L. Endometrial efffects of a TSEC containint BZD/CEE as a menopausal therapy. *Fertil. Steril.* **2009**, *92*, 1018–1024. [CrossRef]

31. Bachmann, G.; Bobula, J.; Mirkin, S. Effects of BZD/CEE on quality of life in postmenopausal women with symptoms of vulvar/vaginal atrophy. *Climacteric* **2010**, *13*, 132–140. [CrossRef] [PubMed]
32. NAMS. Management of symptomatic vulvovaginal atrophy, position statement of the North American Menopause Society. *Menopause* **2013**, *20*, 888–902. [CrossRef] [PubMed]
33. Simon, J.; Nachtigall, L.; Gut, R.; Lang, E.; Archer, D.F.; Utian, W. Effective treatment of vaginal atrophy with an ultra-low-dose estradiol vaginal tablet. *Obstet. Gynecol.* **2008**, *112*, 1053–1060. [CrossRef] [PubMed]
34. Ulrich, L.S.G.; Naessen, T.; Elia, D.; Goldstein, J.A.; Eugster-Hausmann, M. Endometrial safety of ultra-low-dose Vagifem 10 µg in postmenopausal women with vaginal atrophy. *Climacteric* **2010**, *13*, 228–237. [CrossRef] [PubMed]
35. Bachmann, G.A.; Komi, J.O. Ospemifene efectively treats vulvovaginal atrophy in postmenopausal women. *Menopause* **2010**, *17*, 480–486. [CrossRef] [PubMed]
36. Labrie, F.; Martel, C.; Bélanger, A.; Pelletier, G. Androgens in women are essentially made from DHEA in each peripheral tissue according to intracrinology. *J. Steroid Biochem. Mol. Biol.* **2017**, *16*, 9–18. [CrossRef]
37. Kenemans, P.; Speroff, L. Tibolone: Clinicla recommendations and practical guidelines. *Maturitas* **2005**, *51*, 21–28. [CrossRef] [PubMed]
38. Sirotkin, A.V.; Harrath, A.H. Phytoestrogens and their effects. *Eur. J. Pharmacol.* **2014**, *741*, 230–236. [CrossRef]
39. Parkin, D.M. Cancers of the breast, endometrium and ovary: Geographic correlations. *Eur. J. Cancer Clin. Oncol.* **1989**, *25*, 1917–1925. [CrossRef]
40. Speroff, L.; Fritz, M.A. *Clinical Gynecologic Endocrinology and Infertility*, 7th ed.; Lippincott Williams Wilkins: Philadelphia, PA, USA, 2005; p. 1333. ISBN 0-7817-4795-3.
41. Duncan, A.M.; Phipps, W.R.; Kurzer, M.S. Phyto-estrogens. *Best Pract. Res. Clin. Endocrinol. Metab.* **2003**, *17*, 253–271. [CrossRef]
42. Ye, Y.B.; Tang, X.Y.; Verbruggen, M.; Su, Y.X. Soy isoflavones attenuate bone loss in early postmenopausal Chinese women. *Eur. J. Nutr.* **2006**, *45*, 327–334. [CrossRef] [PubMed]
43. Yuan, J.P.; Wang, J.H.; Liu, X. Metabolism of dietary soy isoflavones to equol by human intestinal microflora—Implications for health. *Mol. Nutr. Food Res.* **2007**, *51*, 765–781. [CrossRef]
44. Atkinson, C.; Newton, K.M.; Bowless, E.J.; Yong, M.; Lampe, J.W. Demographic, anthropometric, and lifestyle factors and dietary intakes in relation to daidzein-metabolizing phenotypes among premenopausal women in USA. *Am. J. Clin. Nutr.* **2008**, *87*, 679–687. [CrossRef] [PubMed]
45. Raimondi, S.; Roncaglia, L.; De Lucia, M.; Amaretti, A.; Leonardi, A.; Pagnoni, U.M.; Rossi, M. Bioconversion of soy isoflavones daidzin and daidzein by Bifidobacterium strains. *Appl. Microbiol. Biotechnol.* **2009**, *81*, 943–950. [CrossRef] [PubMed]
46. Somjen, D.; Yoles, I. DT56a stimulates creatine kinase specific activity in vascular tissues of rats. *J. Endocrinol. Investig.* **2003**, *26*, 966–971. [CrossRef] [PubMed]
47. Sánchez-Borrego, R.; Navarro, M.C.; Llaneza, P.; Hormigo, A.; Duran, M.; Mendoza, N. Efficacy and safety of a phyto-SERM as an alternative to hormone therapy. *Climacteric* **2014**, *18*, 350–357. [CrossRef]
48. Labos, G.; Trakakis, E.; Pliatsika, P.; Augoulea, A.; Vaggopoulos, V.; Basios, G.; Simeonidis, G.; Creatsa, M.; Alexandrou, A.; Iliodromiti, Z.; et al. Efficacy and safety of DT56a (Femarelle) compared to hormone therapy in Greek postmenopausal women. *J. Endocrinol. Investig.* **2013**, *36*, 521–526. [CrossRef]
49. Sánchez-Borrego, R.; Mendoza, N.; Llaneza, P. A prospective study of DT56a (Femarelle®) for the treatment of menopause symptoms. *Climacteric* **2015**, *18*, 813–816. [CrossRef]
50. Fait, T.; Borovsky, M. DT56a in treatment of climacteric syndrome in a Central European population sample. *Bratisl. Med. J.* **2021**, *122*, 301–304. [CrossRef]
51. Orleans, R.J.; Li, L.; Kim, M.J.; Guo, J.; Sobhan, M.; Soule, L.; Joffe, H.V. FDA approval of paroxetine for menopausal hot flushes. *N. Engl. J. Med.* **2014**, *370*, 1777–1779. [CrossRef]
52. Nembutsu, H.; Sasa, M.; Kiyotani, K.; Mushiroda, T.; Nakamura, Y. Should CYP2D6 inhibitors be administered in conjunction with tamoxifen? *Expert Rev. Anticancer Ther.* **2011**, *11*, 185–193. [CrossRef] [PubMed]
53. Hellström, A.C.; Muntzing, J. The pollen extract Femal—A nonestrogenic alternative to hormone therapy in women with menopausal symptoms. *Menopause* **2012**, *19*, 825–829. [CrossRef]
54. Fait, T.; Sailer, M.; Regidor, P.A. Prospective observational study to evaluate the efficacy and safety of the pollen extract Sérélys® in the management of women with menopausal symptoms. *Gynecol. Endocrinol.* **2019**, *35*, 360–363. [CrossRef] [PubMed]
55. Llaneza, P.; Garcia-Portilla, P.; Llaneza-Suarez, D.; Armont, B. Depressive disorders and the menopause transition. *Maturitas* **2012**, *71*, 120–130. [CrossRef] [PubMed]
56. Toffol, E.; Keikinheimo, O.; Patronen, T. Hormone therapy and mood in perimenopausal and postmenopausal women: A narrative review. *Menopause* **2015**, *22*, 564–578. [CrossRef]
57. Lederman, S.; Ottery, F.D.; Cano, A.; Santoro, N.; Shapiro, M.; Stute, P.; Thurston, R.C.; English, M.; Franklin, C.; Lee, M.; et al. Fezolinetant for treatment of moderate-to-severe vasomotor symptoms associated with menopause (SKYLIGHT 1): A phase 3 randomised controlled study. *Lancet* **2023**, *401*, 1091–1102. [CrossRef]
58. Sun, A.-J.; Wang, Y.-P.; Gu, B.; Zheng, T.-P.; Lin, S.-Q.; Bai, W.-P.; Wei, Y.; Zhang, S.-F.; Zhang, Y. A Multi-center, Randomized, Controlled and Open Clinical Trial of Heyan Kuntai Capsule and Hormone Therapy in Perimenopausal Women. *Chin. J. Integr. Med.* **2018**, *24*, 487–493. [CrossRef]

59. Taylor-Swanson, L.; Thomas, A.; Ismall, R.; Schnall, J.G.; Cray, L.; Mitchell, E.S.; Woods, N.F. Effects of TCM on symptom clusters during the menopausal transition. *Climacteric* **2015**, *18*, 142–156. [CrossRef] [PubMed]
60. Kim, K.H.; Kang, K.W.; Kim, D.I.; Kim, H.J.; Yoon, H.M.; Lee, J.M.; Jeong, J.C.; Lee, M.S.; Jung, H.J.; Choi, S.-M. Effects of acupuncture on hot flashes in perimenopausal and postmenopausal women—A multicenter randomized clinical trial. *Menopause* **2010**, *17*, 269–280. [CrossRef]
61. Lee, M.S.; Shin, B.C.; Ernst, E. Acupuncture for treating menopausal hot flushes: A systematic review. *Climacteric* **2009**, *12*, 16–25. [CrossRef]
62. Qi, Y. Traditionla Chinese medicine: Perspectives on and treatment of menopausal symptoms. *Climacteric* **2018**, *21*, 93–95. [CrossRef]
63. Liu, T.; Chen, S.; Milke, G.I.; McCarthy, A.L.; Bailey, T.G. Effects of exercise on vasomotor symptoms in menopausal women: A systematic review and meta-analysis. *Climacteric* **2022**, *25*, 552–561. [CrossRef] [PubMed]
64. Moreira, L.D.F.; de Oliveira, M.L.; Lirani-Galvão, A.P.; Marin-Mio, R.V.; dos Santos, R.N.; Lazaretti-Castro, M. Physical exercise and osteoporosis: Effects of different types of exercises on bone and physical function of postmenopausal women. *Arq. Bras. Endocrinol. Metabol.* **2014**, *58*, 514–522. [CrossRef] [PubMed]