ALTERNATIVES OF MENOPAUSAL HORMONE THERAPY

ALTERNATIVE HORMONSKE TERAPIJE U MENOPAUZI

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Summary

Introduction. It has been generally accepted that the benefits of menopausal hormone therapy outweigh the risks, but there are still some concerns about the administration of menopausal hormone therapy, which has introduced alternative treatments. Pharmacological Alternatives. Central alpha-2 agonist clonidine is only marginally more effective than placebo, and significantly less effective than estrogen. Antiepileptic drug gabapentin reduces hot flashes; however, it is less effective than estrogen. Selective serotonin reuptake inhibitors (paroxetine and fluoxetine) and selective noradrenaline reuptake inhibitors (venlafaxine) reduce vasomotor symptoms and improve depression, anxiety and sleep. Results of studies about dehydroepiandrosterone effects on menopausal symptoms are inconsistent and additional investigations are needed. Non-Pharmacological Alternatives. Stellatum ganglion blockade is a successful treatment for reducing vasomotor symptoms in patients with contraindications for menopausal hormone therapy. Efficacy of acupuncture, homeopathy and reflexology should be proved by adequate studies. Phytoestrogens could reduce vasomotor symptoms but to a lesser extent than conventional menopausal hormone therapy. However, they have not been proved yet to provide cardiovascular protection and prevention of osteoporosis, nor they could be recommended instead of traditional menopausal hormone therapy. There is a concern about their undesirable effects. Adequate diet, unchanging body weight within ideal values and adequate physical activities have beneficial long-term effects, first of all on preservation of bone density. Alternatives for Atrophic Changes of Vaginal Epithelium. Menopausal symptoms resulting from vaginal atrophy could be resolved by use of hydrophilic preparations, lubricants and topical lidocaine cream or 4% lidocaine water solution for dyspareunia. Conclusion. If there are contraindications to menopausal hormone therapy or patients are unwilling to take hormone therapy, alternative treatments, which can also solve menopausal symptoms, should be considered. Key words: Estrogen Replacement Therapy; Perimenopause; Complementary Therapies; Treatment Outcome; Pharmaceutical Preparations; Phytoestrogens

Introduction

Benefits of menopausal hormone therapy (MHT) are clear: it is efficient in resolving menopausal symp-
On the other hand, there are numerous reports showing that MHT is associated with the risk for developing unwanted complications. In spite of the statement that the benefits from MHT are more likely to overweight the risks in symptomatic women under 60 years of age or if it is started within 10 years after menopause [1–3], the concern which is associated with the use of MHT is understandable. [4]. The aim of this article is to present current alternatives to MHT in the treatment of menopausal symptoms (Table 1).

Pharmacological Alternatives

**Alpha-2 Agonists – Clonidine**

In spite of its popularity in the western countries as an alternative therapy for the menopausal vasomotor problems, centrally active alpha-2 agonist clonidine is only marginally more effective than placebo, but considerably less efficient than estrogen [5]. Undesirable effects of clonidine are dry mouth, sense of dryness and insomnia [3].

**Gabapentin – Antiepileptic**

Antiepileptic gabapentin reduces hot flushes, but to the lesser extent than estrogen does [6]. It is a possible alternative for patients with natural or artificial menopause, who cannot receive estradiol, or for the patients who do not want to receive hormone replacement therapy. It is administered at dose of 600 to 2400 mg/day in divided doses, with gradually increased doses. Side effects are somnolence, sense of dryness and weakness, peripheral edemas, being most prominent during the first two weeks of the therapy [7]. A recent trial of gastroretentive gabapentin in the form of tablet with gastric retention up to 10 hours, which gradually releases gabapentin allowing optimal resorption, showed that gabapentin in this form is a modestly effective non hormone therapy for the treatment of moderate to severe menopausal vasomotor problems. This route of administration allows less frequent daily administration (600 mg am/1200 mg pm), better medication titration, with fewer side effects [8].

**Selective Serotonin Reuptake Inhibitors and Serotonin-norepinephrine Reuptake Inhibitors**

Since serotonin is known as the “hormone of happiness”, it is logical to think that selective serotonin reuptake inhibitors (SSRI) and serotonin-norepinephrine reuptake inhibitors/selective noradrenaline reuptake inhibitors (SNRI) could be useful in the management of menopausal symptoms. SSRI used for such purposes are fluoxetine (20 mg/day), paroxetine (12.5 – 25 mg/day), medicaments that have already been used in psychiatry. SSRI are modestly effective in the management of menopausal symp-
toms, escitalopram being the most effective [9]. They reduce the frequency and severity of hot flushes, improve depression, anxiety and sleeping disturbances.

Side effects of such therapy are nausea, dizziness, dry mouth, constipation, somnolence, sweating, decreased libido, sexual dysfunction and rush, but with the time and dose titration, all these side effects disappear [9, 10].

SNRI used for such purposes is venlafaxine taken at a dose of 37.5 mg twice daily, with similar side effects [4]. Its analogue (desvenlafaxine succinate) is also efficient, with fewer side effects [11]. It seems that SSRI and SNRI could be a reasonable alternative treatment for menopausal vasomotor symptoms in women who cannot take the menopausal hormone therapy or are concerned about the long-term effects of estrogen, but those medications are not an optimal choice for the patients with no contraindication for conventional MHT.

**Dehydroepiandrosterone**

The levels of dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulphate (DHEASO4) fall in the postmenopausal period. DHEA is a precursor for sex steroids. DHEA does not improve menopausal symptoms, but raises the levels of testosterone. Other studies have shown positive effects on bone density, cognitive functions, libido and improvement of vaginal atrophic changes [12]. Beneficial effects of DHEA on fertility have been reported recently, but further studies are needed for definitive conclusions [4].

Adverse cardiovascular effects are possible due to unfavorable effects of DHEA on lipid profile (decreasing the levels of high density lipoproteins) [10].

Current guidelines are against the routine administration of DHEA and testosterone in patients with low androgen levels due to hypopituitarism, surgical menopause, glucocorticoid administration and other conditions associated with low androgen levels because there are no adequate long-term studies about the effectiveness and safety of such therapy [13].

**Non-Pharmacological Alternative Treatments**

**Stellate Ganglion Blockade**

Stellate ganglion blockade means an injection of local anesthetic into the stellate ganglion. This intervention is successful in resolving vasomotor menopausal problems in patients with contraindications for menopausal hormone therapy. Complications are few [14].

The other possibilities of non-pharmacological treatments for vasomotor menopausal problems are acupuncture, homeopathy, reflexology (application of pressure to specific points of the feet, hands and ears), but the efficiency of such treatments has not been proved by adequate studies [4].

**Phytoestrogens**

It is generally believed that complementary therapies are safer and more natural alternatives
Blokada gangliona
Dezvenlafaksin sukcinat

Benefits of those substances are small: they can act as weak agonists stimulating ER. Phytoestrogens have no impact on the endometrium, vagina, nor unwanted effects during two years of use [16].

Phytoestrogens reduce the levels of low density lipoproteins, they do not affect high density lipoproteins, that being true only for intact soya proteins. Phytoestrogens may ameliorate insulin resistance and could be considered a beneficial dietary factor for prevention and management of type 2 diabetes [17]. On the other side, some studies have shown that phytoestrogens may have beneficial effects on bone density (improving the density of vertebra, with no effects on the hip) and on cardiovascular system, but there is no strong evidence to support this [1].

Phytoestrogens have no impact on the endometrium or symptoms of genital atrophy. A protective effect on breast is possible [10]. Many plants are used traditionally for menopausal symptoms, but adequate studies to prove their efficacy are still lacking. The placebo effect must be taken into consideration [4].

Meta-analyses of reported trials have showed that so far there is no adequate evidence to recommend phytoestrogens instead of conventional MHT, or to support their role in prevention and treatment of cardiovascular diseases [15]. On the other hand, many herbal medications do have pharmaceutical performances, thus they might have undesirable effects. That is why phytoestrogens should be avoid-

than the traditional menopausal hormone therapy, but the efficacy and real safety of majority of these preparations have not been proved yet [4].

Phytoestrogens are nonsteroidal plant substances with estrogen activity. The major classes are isoflavones (the most potent), lignans and coumestans. The term phytoestrogens also includes stilbenes, flavonones, flavonols and flavones [15]. Isoflavones can be found in soya, red clover and probably in other legumes such as peas and beans. Oils extracted from seeds are rich in lignans (e.g. from flaxseed, bran and whole grains, vegetables, legumes, fruits). Phytoestrogens, structurally not identical to human hormones, have mixed estrogenic and anti-estrogenic effects, which depend on the tissue. These effects are mediated via estrogen receptors (ER) (α- and β-), and possibly G protein coupled estrogen receptor (GPER). It is postulated that phytoestrogens act as selective modulators of estrogen receptors (SERM): during premenopausal period, when the endogenous estrogen levels are high, they demonstrate anti-estrogenic effects; in postmenopausal period, when the endogenous estrogen levels are low, phytoestrogens act as weak agonists stimulating ER. Phytoestrogens show higher affinity for β-ER than for α-ER: estrogenic activity is more expressed in the central nervous system, vasculature, bones and skin; it is less on the uterine level and breast. Experimental studies have reported beneficial effects of phytoestrogens on the endothelium, vascular smooth muscle and extracellular matrix, as well as on the lipid profile, inflammation, angiogenesis and tissue damage by reactive oxygen species, which could delay atherosclerosis. Considering all the above mentioned, it seems that phytoestrogens could be ideal alternatives to traditional menopausal therapy.

The conclusions of clinical studies are slightly different. Benefits of those substances are small: they can reduce hot flashes, but not significantly, and to the lesser extent than conventional MHT. Meta-analysis of 43 randomized controlled trials including 4,364 participants has failed to confirm the efficacy of phytoestrogens to reduce vasomotor menopausal problems although isoflavons derived from soya, with the most potent estrogenic action, deserve further investigation. Significant placebo effect in reduction of vasomotor symptoms was noticed in the majority of included trials (from 1% to 50%). This meta-analysis has also confirmed that there are no proofs for estrogenic stimulation of endometrium, vagina, nor unwanted effects during two years of use [16].

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Table 1. Alternative treatments for menopausal problems

<table>
<thead>
<tr>
<th>Alternative pharmacological therapies/Alternative farmakološke terapije</th>
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<tbody>
<tr>
<td>- Alpha 2 agonist - clonidine/Alfa 2 agonist - klonidin</td>
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<td>- Gabapentin/Gabapentin</td>
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<tr>
<td>- Selective serotonin reuptake inhibitors (SSRI) and serotonin - norepinephrin (noradrenaline) reuptake inhibitors (SNRI)</td>
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<tr>
<td>Selectivni inhibitori preuzimanja serotoninina i inhibitori preuzimanja serotoninina - nerepinefrina (noradrenalina)</td>
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<tr>
<td>- Paroxetine/Paroksetin - Venlafaxine/Venlafaksin</td>
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<tr>
<td>- Fluoxetine/Fluoksetin - Desvenlafaxine succinate/Dezvenlafaksin sukcinat</td>
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<td>- Dehydroepiandrosterone/Dehidroepiandrosteron</td>
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<tr>
<th>Non-pharmacological treatments/Nefarmakološki tretmani</th>
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<tr>
<td>- Ganglion stellate blockade for vasomotor symptoms/Blokada gangliona stelatum za vazomotorne simptome</td>
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<tr>
<td>- Physiological activity/Fizička aktivnost</td>
</tr>
<tr>
<td>- Vitamin D3, calcium, omega 3 supplementation/Suplementacija vitamina D, kalcijuma i omega 3 kiselinama</td>
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<tr>
<th>Alternative treatments for atrophic changes (dyspareunia)/Alternativni tretmani atrofičnih promena (dispareunije):</th>
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<tr>
<td>- Vaginal moisturizers/Vaginalni hidrofilni preparati</td>
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<td>- Vaginal lubricants/Vaginalni lubrikanti</td>
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<tr>
<td>- Topical lidocaine for dyspareunia /Površno lidokain za dispareuniju</td>
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ed in circumstances when estrogen is contraindi-
cated: in the presence of estrogen dependent tumors, 
 thromboembolism and cardiovascular diseases. The 
 attention should be paid to possible hepatotoxicity 
 caused by some of those plants [18], as well as pos-
 sible interactions with pharmacological medications.

Physical Activity, Diet and Supplements 
as Alternatives to MHT

Changes in the lifestyle cannot help too much in 
 resolving actual menopausal symptoms. On the 
 other hand, adequate diets, unchanging body weight 
 within optimal limits and adequate physical activity 
 have favorable long-term effects.

Introduction of optimal diet and adequate physical 
 activity should be a part of routine management of all 
 women in perimenopausal period and later [1, 19].

It is important to maintain body weight within 
 optimal limits in order to preserve bone density and 
 decrease the incidence of fractures in the postmen-
 opausal period. Weight gain, as well as its un-
 planned loss, is associated with increased incidence 
 of fractures of different localization. Planned body 
 mass reduction is associated with a slightly in-
 creased incidence rate of lower limb fracture, but 
 the incidence of hip fracture is lower [20].

Physical activity can alleviate menopausal 
 symptoms, and very important factors are the type 
 of personality and active life style [21]. A recent 
 study [22], examining the association of demo-
 graphic, lifestyle parameters and perceived sever-
 ity of menopausal symptoms, has shown that regu-
 lar exercises (three times a week) can also alleviate 
 menopausal symptoms, measured by Greene cli-
 macteric score, with lowered total and somatic sub-
 scores, especially psychological and sexual sub-
 scores. More frequent exercises (both aerobic and 
 non aerobic) reduced the severity of menopausal 
 symptoms although sexual and vasomotor subscores 
 remained unchanged. It was interesting that mothers 
 of three and more children had lower Greene score, 
 which was also reported in other studies [23].

A recent meta-analysis examining the effective-
 ness of physical activity on menopausal symptoms 
 reduction reported that evidence was not strong 
 enough to show that exercises were an effective treat-
 ment for vasomotor symptoms, or that they were 
 more effective than yoga or conventional MHT [24]. 
 Low moderate intensity physical activity during post-
 menopausal period decreases the inflammatory cy-
 tokine plasma levels, which correlates with more 
 favorable reproductive hormone profile comparing 
 with the sedentary way of life [25]. It has also been 
 reported that physical activity increases bone den-
 sity, improves bone strength and prevents bone loss 
 in the elderly [26].

A recent study has reported a favorable effect of 
 physical activity on the mammographic density, better 
 lobular involution among postmenopausal women and 
 a possible protective effect on the breast [27].

Decreased estradiol levels after surgical or natu-
 ral menopause cause decreased expression of genes 
 for effective energy consumption, as well as genes 
 for catabolism of lipids. This is, at least partially, the 
 cause of obesity and its consequences after meno-
 pause. Animal experiments have shown that physical 
 activity in combination with restrictive diet prevents 
 the development of metabolic syndrome induced by 
 high caloric diet in association with estrogen defi-
 ciency or artificial menopause [28, 29]. Human stud-
 ies have confirmed this conclusion [30].

Physical activity and omega-3 supplementation 
 in the postmenopausal period have synergistic ef-
 fect in attenuating inflammation and augmenting 
 bone density in postmenopausal osteoporosis [31].

Common sense solutions could be effective in the 
 treatment of vasomotor problems: cooling and cold 
 drinks, avoidance of hot and alcoholic drinks as well 
 as hot and spicy food, smoking cessation, excessive 
 weight loss and layering of clothing [3, 4].

Alternative Treatments for Vulvovaginal 
 Atrophy

Menopausal symptoms caused by atrophic 
 changes of vaginal epithelium could be managed by 
 vaginal use of hydrophilic preparations, moistur-
 izers, rehydrating vaginal tissue, which are a good 
 alternative to vaginal estrogen, acting more physi-
 ologically than vaginal gels [1, 4].

Recent studies have demonstrated that topical 
 lidocaine cream application is very effective before 
 speculum examination in postmenopausal women 
 [32] or 4% aqueous lidocaine solution for dyspareu-
 nia [33]. Lubricants and regular sexual activity could 
 also be helpful [34, 35]. Thereby, special attention 
 should be paid to the preservation of normal vaginal 
 flora. Future studies of vaginal microbiome could 
 become the base for the new treatment options.

Conclusion

If there are contraindications for menopausal hor-
 mone therapy or the patient does not want to take 
 hormones, alternative treatments for menopausal 
 symptoms should be considered. Alternatives to 
 menopausal hormone therapy include pharmaco-
 logical treatments (clonidine, gabapentin, selective 
 serotonin reuptake inhibitors and serotonin/norepine-
 phrine reuptake inhibitors, dehydroepiandrosterone) 
 and non-pharmacological alternatives (ganglion stel-
 latum blockade for vasomotor problems, phytoestro-
 gens, physical activity and adequate diet, as well as 
 omega-3, vitamin D and calcium supplementation).

Further studies are needed to confirm the effi-
 cacy and safety of some complementary treatments. 
 All mentioned alternatives are less successful in 
 treatment of menopausal symptoms than conven-
 tional menopausal therapy.

Adequate diets, unchanging body weight within 
 optimal limits and adequate physical activity have
favorable long term effects on bone density in the first place.

Menopausal symptoms resulting from atrophic changes of vaginal epithelium could be treated by vaginal use of hydrophilic preparations, moisturizers, lubricants and topical lidocaine cream or 4% lidocaine aqueous solution for dyspareunia.

References


l lipid profile in overweight and obese postmenopausal women in an experimental, nonrandomized, open-label, prospective controlled trial. Menopause. 2015;22(11):1215-23.


