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Review article

Hormone therapy for postmenopausal women—An unanswered issue

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ABSTRACT

Menopause is a biological and natural process that occurs as part of aging in women and is secondary to ovarian failure with resultant estrogen deficiency; therefore, menopause should not be considered as a disease. However, there is no doubt that estrogen deficiency induces general psychological and physical changes, and that postmenopausal women will experience many health-related issues and problems, including osteoporotic fractures, coronary heart disease (CHD), and most importantly for the quality of life (QOL) and vasomotor symptoms (VMS) such as hot flashes and night sweats. Hormone therapy (HT) is very effective in the management of postmenopausal women with symptoms. With the large number of patients being treated with HT, especially the combination of estrogen and progestin therapy (EPT) in the Women's Health Initiative (WHI) study, clinicians now recognize the potential adverse effects of EPT. Although this concept is much clearer now, some women might still benefit from short-term HT, especially for young postmenopausal women. In this review, some health issues of postmenopausal women, especially alternative therapies are discussed.

Introduction

Menopause is a biological process that occurs as a part of aging in women. Aging is the natural progression of changes in the structure and function of bodily systems that occurs as a function of the progress of time and in the absence of disease. Therefore, menopause should not be considered as a disease. However, menopause results in a hypoestrogenic state of the body, and subsequently may adversely affect estrogen target tissues, including the brain, skeleton, and skin, as well as the cardiovascular and genitourinary systems.[1] The reaction of target tissues to estrogen deficiency, with the resultant frequency and severity of climacteric symptoms, varies significantly among women. These climacteric symptoms frequently bother perimenopausal (the menopausal transition) and/or post-menopausal women, resulting in severe interference in their quality of life (QOL). The concept of hormone therapy (HT), including estrogen-only therapy (ET) or a combination of estrogen and progestin therapy (EPT) after menopause is based on the clinical observations that elderly women with very low serum levels of estrogen have a higher incidence of osteoporotic fractures, coronary heart disease (CHD), and, most importantly for the QOL and vasomotor symptoms (VMS) such as hot flashes and night sweats. The most commonly prescribed hormone for women with a uterus is estrogen, either as ET or EPT. The principal indication for the use of EPT is the presence of a uterus.[2]

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Adverse events with hormone therapy, especially EPT, for chronic diseases in postmenopausal women

Estrogen deficiency is the main cause of postmenopausal osteoporosis,[3] and it leads to an increase in bone remodeling, resulting in an imbalance between bone resorption and formation; this is reflected in a decrease in the bone mineral density (BMD) and an increase in fracture risk. HT reverses these changes in women in both the early and late phases of the postmenopausal period. However, the role of long-term postmenopausal HT in the prevention and management of osteoporosis has become controversial,[4,5] especially after the publication of the Women's Health Initiative (WHI) study of EPT[6] and its sister study of ET.[7] The study population consisted of women in the age group of 50–79 years, many of whom had cardiovascular (CV) risk factors. Women were not selected with low BMD, unlike most osteoporosis trials. The WHI was the first large, randomized clinical trial to show that EPT reduces osteoporotic fractures, including a 34% reduction in both vertebral and hip fractures.[6] This reduction occurred even though the study subjects were at low risk for fractures.[6] In addition, the ET trial also showed substantial reductions in subsequent osteoporotic fractures.[7]

However, there are many endpoints, and controversy exists about the appropriate adjusted confidence intervals. Overall, the increase in stroke was 8 per 10,000 person-years, although the absolute risk is low in women in their 50s and rises with age. An increased risk of CV events was shown with EPT, especially in those starting treatment when they were older than 70 years.[6] In the EPT study, there was an increase in breast cancer by 5 years in 8 per 10,000 person-years.[6] This increase was matched by a similar reduction in other major cancers, and there were no changes in overall cancer or mortality rates.[6] The ET study was stopped after 6.8 years because of stroke events, but by then had shown a reduction ($p = 0.06$) in breast cancer of 7 per 10,000 person-years.[7] These data suggest a different risk profile for opposed therapies compared with an unopposed estrogen and for older versus younger women, especially the relationship between the use of EPT or ET and the risk of breast cancer.[8] Many authors tried to respond to the conflicted data of HT on the risk of breast cancer. For example, Chlebowski and Anderson used the underlying biology to provide a framework for understanding the mechanisms mediating these hormone effects.[8] Shapiro S and colleagues evaluated the evidence for causality in the WHI studies using generally accepted causal criteria and found that the findings did not adequately satisfy the criteria of bias, confounding, statistical stability and strength of association, duration-response, internal consistency, external consistency, or biological plausibility; therefore, the authors still failed to clarify these, since the WHI did not establish that it does.[9]

A recent Cochrane database systematic review (Table 1), including 23 studies involving 42,830 women (70% of women derived from WHI 1998 and HERS 1998, most participants with at least some degree of co-morbidity, mean age >60 years), found that continuous EPT increased the risk of a coronary event, venous thromboembolism, stroke, breast cancer, gallbladder disease and death from lung cancer in relatively healthy postmenopausal women (who are generally fit, without overt disease), and that long-term ET also significantly increased the risk of venous thromboembolism, stroke and gallbladder disease, except breast cancer, suggesting either EPT or ET is not indicated for primary or secondary prevention of cardiovascular disease or dementia, nor for preventing the deterioration of cognitive function in postmenopausal women.[10]

From the WHI results, one might suggest that in women with osteoporosis and CV risk factors, both EPT and ET should be avoided, and for the purpose of managing and treating osteoporosis, other anti-osteoporosis agents would be a better choice.[4,11] The use of EPT or ET might remain an option only for short-term early use around menopause in symptomatic younger women, although there are insufficient data to assess the risk of long-term HT use in perimenopausal women or postmenopausal women younger than 50 years of age.[10]

Table 1
The summary of Cochrane database systematic review.

Medication	Events	Duration of hormone use (years)	Risks	95% CI
EPT	Death from any cause		OR 1.06	0.93–1.21
	Coronary event	1	AR 4	3–7
	Venous thromboembolism	1	AR 7	4–11
	Stroke	3	AR 18	14–23
	Breast cancer	5.6	AR 23	19–29
	Death from breast cancer	11	RR 1.98	1.00–3.95
	Gallbladder disease	5.6	AR 27	21–34
	Death from lung cancer[a]	5.6	AR 9	6–13
ET	Death from any cause		OR 1.02	0.90–1.15
	Venous thromboembolism	1–2	AR 5	2–10
	Venous thromboembolism	7	AR 21	16–28
	Stroke	7	AR 32	25–40
	Gallbladder disease	7	AR 45	36–57

AR = absolute risk per 1000; CI = confidence interval; EPT = estrogen and progestin therapy; ET = estrogen-only therapy; OR = odds ratio; RR = risk ratio.
[a] After 5.6 years of use and an additional follow-up of 2.4 years.

The recommendations on postmenopausal hormone therapy and preventive strategies for midline health from the International Menopause Society (IMS)[12] are shown below. First, the safety of HT largely depends on age. Second, new data and re-analyses of older studies by women's age show that for most women, the potential benefits of HT given for a clear indication are many and the risks are few when initiated within a few years of menopause. A recent open label, randomised controlled trial (1006 healthy women aged 45-58 years) – after 10 years of randomised treatment showed that women receiving HT early after menopause had a significantly reduced risk of mortality, heart failure or myocardial infarction, without any apparent increase in risk of cancer, venous thromboembolism or stroke.[13] Third, there is increasing evidence that non-oral routes of HT have little or no increased risk of thromboembolism and would be the regimens of choice in women with thromboembolic risk factors, if HT was considered appropriate. Fourth, there is considerable evidence from laboratory, animal, observational and randomized trials of a therapeutic window of benefits for cardio- and neuro-protection if HT is prescribed in midlife from near menopause in symptomatic women.[11] However, the U.S. Preventive Services Task Force (USPSTF) still recommends against either the use of EPT or ET for the prevention of chronic conditions in postmenopausal women (Grade D recommendation).[14]

The North American Menopause Society (NAMS) also recommended the initiation of HT around the time of menopause to treat menopause-related symptoms and to prevent osteoporosis in women at high risk of fracture and that the more favorable benefit-risk ratio for ET allows more flexibility in extending the duration of use compared with EPT, where the earlier appearance of increased breast cancer risk precludes a recommendation for use beyond 3 to 5 years.[15] A recent report of an extended follow-up of the WHI trial, which was conducted to assess the long-term effects of estrogen use on invasive breast cancer incidence, tumor characteristics and mortality provided reassurance for women with hysterectomy seeking relief of climacteric symptoms in terms of the effects of estrogen use for about 5 years on breast cancer incidence and mortality, although the results failed to support the use of estrogen breast cancer risk reduction.[16]

Alternative therapies for osteoporosis

Osteoporosis is a systemic bone disease,[11] and the clinical consequence of osteoporosis is fracture. Vertebral fracture is an important source of morbidity in terms of pain and spinal deformity.[17] Hip fracture is associated with the worst outcomes and is widely regarded as a life-threatening event in the elderly.[17] For many years, HT was the mainstay in osteoporosis prevention in postmenopausal women, until WHI trials raised serious safety concerns,[6,7] resulting in a big drop in EPT or ET use and its demotion by regulatory authorities to the second-line treatment for osteoporosis prevention in postmenopausal women.[18] How effective are these alternative therapies, are they any safer than HT, and how do their costs compare?[19] It is not easy to respond to these questions. The classical triad for consideration in osteoporosis is morbidity, mortality, and cost.[17] In fact, many alternative therapies are available for the treatment and prevention of osteoporosis, including calcium and vitamin D, bisphosphonates, selective estrogen receptor modulators (SERM, for example, raloxifene and bazedoxifene), calcitonin, (1-34) parathyroid hormone (hPTH 1-34), strontium ranelate, and mono-antibodies (denosumab) against receptor activator of nuclear factor κB ligand (RANKL).[19]

Before discussing anti-osteoporosis agents, at least 3 points should be emphasized: efficacy, adverse event, and cost.

Efficacy of alternative therapies in the management of postmenopausal women with osteoporosis

The efficacy could be obtained in recent reviews.[8,10,11] All these osteoporosis treatments were shown to be positive in the prevention of further fracture. All treatments were effective and significant in decreasing the risk of vertebral fracture in postmenopausal women with established osteoporosis and prevalent vertebra fractures. The relative and absolute reductions in the risk of vertebral fracture in the osteoporosis trials ranged, respectively, from 30% to 70% relative risk reduction (Table 2) and 1.8% to 10.9% absolute risk reduction (Table 3). However, in the subgroup of postmenopausal women with osteoporosis but without prevalent vertebral fractures, the level of evidence was low, since not all studies confirmed the efficacy. The efficacy was even more questionable if these postmenopausal women were diagnosed with osteopenia only.

On the other hand, the data supporting the efficacy of these drugs in preventing hip fracture is very deficient, and suggest that these alternative treatments for osteoporosis were indeed inferior to HT, as shown by the significant relative risk reduction with HT (up to 34%) in the WHI report (Tables 2 and 3).[6,7] From the data available in the literature, the relative and absolute reductions in the risk of hip fracture in the osteoporosis trials ranged, respectively, from 30% to 51% relative risk reduction (Table 2) and 0.3% to 2.1% absolute risk reduction (Table 3).

Adverse events of alternative therapies in the management of postmenopausal women with osteoporosis

The adverse effects were considered, and included two parts: one was frequency and the other, severity. The incidence (or frequency) of adverse effects can be divided into five categories based on numbers per 10,000 persons (Table 4), including category 1 (very rare), category 2 (rare), category 3 (uncommon or infrequent), category 4 (common or frequent), and category 5 (very common) with an incidence of more than 10%.[17] The severity of adverse effects can be divided into 6 categories, based on hospitalization, incapacity, permanent sequelae and fetal outcomes (Table 4).[17] In summarizing the adverse events of all agents available for osteoporosis treatment, the prevalence of adverse events with these agents was generally less than 10%, and nearly all of them had category 1 severity.

The adverse events of SERMs included venous thromboembolism, pulmonary embolism, fatal strokes, hot flashes, and leg cramps, although these CV adverse events seemed to be race and age dependent.[20,21] A recent report from Japan[22] suggested no significantly increased risk of stroke among Japanese women from the three reference regions, with 1 year of raloxifene use compared with the Japanese epidemiological data (0.68 (95% CI, 0.45-1.02), 0.54 (95% CI, 0.35-0.83), and 0.82 (95% CI, 0.54-1.24)). In addition, the same study[22] also showed no significantly increased or decreased risk of stroke among Japanese population in different age groups (incidence rate ratio: 2.83 (95% CI, 0.91-8.81) and 3.43 (95% CI, 0.9612.28) in the 50-59 years group; 0.2 (95% CI, 0.03-1.45) and 0.24 (95% CI, 0.03-1.77) in the 60-69 years group; 0.79 (95% CI, 0.46-

Table 2
Relative risk reduction in the vertebral and hip fracture trials.

Medication	Study	Vertebral fracture	Study	Hip fracture
		RRR (%)		RRR (%)
Raloxifene	MORE	30		
Lasofoxifene	PEARL	40		
Strontium Ranelate	SOTI	41	TROPOS	36
Risedronate	VERT-NA	41		
Bazedoxifene	No acronym	42		
Alendronate	FIT	47	FIT	51
Risedronate	VERT-MN	49	HIP	30
Ibandronate	BONE	62		
Teriparatide	FPT	65		
Denosumab	FREEDOM	68	FREEDOM	40
Zoledronic acid	HORZON	70	HORIZON	41

BONE = oral iBandronate Osteoporosis Vertebral Fracture Trial in North America and Europe; FIT = Vertebral Fracture Arm of the Alendronate Fracture Intervention Trial; FPT = Fracture Prevention Trial; FREEDOM = Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months; HIP = Hip Intervention Program; HORIZON = Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly; MORE = Multiple Outcomes of Raloxifene Evaluation; PEARL = Postmenopausal Evaluation and Risk Reduction with Lasofoxifene; RRR = relative risk reduction; SOTI = Spinal Osteoporosis Therapeutic Intervention; TROPOS = Treatment of Peripheral Osteoporosis Study; VERT-MN = Vertebral Efficacy with Risedronate Therapy Multinational Study; VERT-NA = Vertebral Efficacy with Risedronate Therapy North American Study.

Table 3
Absolute risk reduction in the vertebral and hip fracture trials.

Medication	Study	Vertebral fracture	Study	Hip fracture
		ARR (%)		ARR (%)
Bazedoxifene	No acronym	1.8		
Lasofoxifene	PEARL	3.9		
Denosumab	FREEDOM	4.8	FREEDOM	0.3
Ibandronate	BONE	4.9		
Risedronate	HIP	5	HIP	1.1
Raloxifene	MORE	6.5		
Alendronate	FIT	7	FIT	1.1
Zoledronic acid	HORIZON	7.6	HORIZON	1.1
Teriparatide	FPT	9		
Ibandronate	VERT-MN	10.9		
Strontium ranelate	SOTI	11.9	TROPOS	2.1

ARR = absolute risk reduction; BONE = oral iBandronate Osteoporosis Vertebral Fracture Trial in North America and Europe; FIT = Vertebral Fracture Arm of the Alendronate Fracture Intervention Trial; FPT = Fracture Prevention Trial; FREEDOM = Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months; HIP = Hip Intervention Program; HORIZON = Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly; MORE = Multiple Outcomes of Raloxifene Evaluation; PEARL = Postmenopausal Evaluation and Risk Reduction with Lasofoxifene; SOTI = Spinal Osteoporosis Therapeutic Intervention; TROPOS = Treatment of Peripheral Osteoporosis Study; VERT-MN = Vertebral Efficacy with Risedronate Therapy Multinational Study.

Table 4
The classification of adverse effects based on frequency (incidence) and severity.

Category	Frequency (incidence)	Per 10,000 persons	Severity
1	Very rare	< 1	All other outcomes of less severity
2	Rare	1–10	Hospitalization $\leq$ 2 days or incapacity $\leq$ 7 days
3	Uncommon or infrequent	10–100	Hospitalization $>$ 2 days or permanent sequelae $\leq$ 20% or incapacity $>$ 7 days
4	Common or frequent	100–1000 (1–10%)	Fetal outcome $<$ 1% or permanent sequelae $\geq$ 20%
5	Very common	$>$1000 ($>$10%)	Fetal outcome between 1% and 10%
6			Fetal outcome more than 10%

1.37) and 0.56 (95% CI, 0.31-1.01) in the 70-79 years group; and 0.52 (95% CI, 0.23-1.17) and 0.41 (95% CI, 0.18-0.94) in the more than 80 years group).

The adverse events with bisphosphonates use include osteonecrosis of the jaw, atrial fibrillation (association with bisphosphonates unproven), atypical femur fractures, esophageal cancer (association with bisphosphonates unproven), gastric ulcer and upper gastrointestinal intolerance, post-dose symptoms (influenza-like symptoms, such as headache, pyrexia, myalgia, and arthralgia) and elevated serum creatinine levels.

The adverse events with calcitonin use included stinging or tingling of the nasal passage, nasal mucosal erythema and minor bleeding, sneezing, rhinitis, and nausea.

The adverse events with denosumab use included serious infections of the skin and urinary tract, a dermatologic reaction, such as dermatitis, eczema, and rashes, cellulitis, including erysipelas, and osteonecrosis of the jaw.

Cost of alternative therapies in the management of postmenopausal women with osteoporosis

When we consider the cost of these alternative treatments for osteoporosis, we find that the lowest cost was for HRT, and the most expensive drug was teriparatide. The cost of monthly teriparatide in Taiwan is nearly NT$15,000 (US$500), but that of monthly EPT is only NT$300 (US$10). We recommend that therapeutic decisions for postmenopausal women with osteoporosis, especially those who have a prevalence of vertebral fracture, should be based on a balance between benefits and risks of treatment. This consideration should be individualized, since no single agent is appropriate for all patients.

Conventional HRT is still a most effective therapy for climacteric symptoms in postmenopausal women

Furthermore, conventional HT has been reported to be the most effective therapy for climacteric syndromes—especially VMS—and may be the first-line treatment in use for relief of VMS. For example, a meta-analysis of 21 randomized, double-blinded, placebo-controlled trials found that systemic ET/EPT significantly reduced both hot flash frequency and severity compared with a placebo, with reduction rates up to 77% and 87%, respectively.[23] A recent report on the WHI study lent further evidence to the above finding, showing that 85.7% of subjects on EPT, compared with 57.7% of women on a placebo, had relief from hot flashes, and 77.6% of subjects on EPT, compared with 57.4% of women on a placebo, had relief from night sweats.[24] However, the relief of VMS was not equivalent to the improvement of health-related quality of life (HRQOL). For example, Eviö and colleagues found that among elderly women, HT use has a statistically significantly positive effect on some dimensions of HRQOL, but not on HRQOL overall.[25] Therefore, they concluded that improving HRQOL is not an indication for HT use in elderly postmenopausal women. The WHI trial also showed that neither EPT nor ET had a clinically meaningful effect on HRQOL in postmenopausal women.[26–28]

Grady commented that women with VMS must weigh the risks associated with treatment against the benefit of symptom relief. Since VMS occur in about two-thirds of women and are very distressing in 10-20%, new treatments that are highly effective and safe are required.[29]

Although the post-WHI turmoil was actually focused on the risks of therapy, data from more recent publications "surprisingly" indicated that risk may vary with the type of hormone, its dosage, route of administration, duration of treatment, and patient age, suggesting that there were still some doubts about the use of HT and the increased CV risk.[30,31]

Alternative therapies for menopause-related symptoms

Since approximately 40% of women will seek medical advice for the management of menopausal symptoms and WHI influenced many women to discontinue either ET or EPT,[32] all push these symptomatic women to use alternative medicine or therapies. The National Center for Complementary and Alternative Medicine has divided alternative medicine into 5 categories, including biologically based, mind-body, energy, manipulative, and body-based therapies, and whole medical systems.[33] Among these, whole medical systems are much more complicated, since they involve complete systems of theory and practice that have evolved independently from allopathic medicine and are often culturally based.[32] For example, whole medical systems in the eastern world were significantly different from those in the western world; and the former includes those from China (traditional Chinese medicine) and India (Ayurvedic medicine), but the latter includes homeopathy and naturopathy. Although some individual trials suggest a benefit for certain therapies, a systematic review did not support the effectiveness of any complementary and alternative therapy for the management of menopausal symptoms[32]; suggesting these potential therapies warrant a further well-designed study to determine the effectiveness and adverse events. By contrast, the selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs), clonidine, and gabapentin trials provide evidence of efficacy for menopausal hot flashes; however, effects are really less than for ET or EPT,[34] suggesting that these medications may be most useful for highly symptomatic women who cannot receive ET or EPT but are not optimal choices for most women.

Tibolone is another option for the treatment of VMS,[35] is available in Europe, Canada, and some other countries in Latin America and Asia, including Taiwan.[36] Tibolone is a synthetic drug with many active metabolites with properties similar to estrogen, androgen and progesterone, contributing to a lower incidence of uterine bleeding compared to conventional HT.[35] Although many studies show that its efficacy is comparable to that of HT, its use carries risks similar to those of HT in breast and endometrial tissues.[37] A recent Cochrane database systematic review evaluated the effectiveness and safety of tibolone in treating postmenopausal women and concluded the following: (1) tibolone, used at the daily dose of 2.5 mg, may be less effective than EPT in alleviating menopausal women, although the incidence of vaginal bleeding is reduced; (2) available data on the long-term safety of tibolone is concerning given the increase in the risk of breast cancer in women who had breast cancer in the past, and in a separate trial, the increase in the risk of stroke in women whose mean age was more than 60 years; (3) similar concerns may exist for EPT, but the overall benefit-risk profile of EPT is better known and more directly related

to women with menopausal symptoms.[38] Umland and Falconieri announced that tibolone may not be any safer than HT itself.[37] For these reasons, the use of tibolone in place of conventional HT for VMS treatment should be weighted in benefits/risks ratio.

Conclusion

Taken together, either EPT or ET for postmenopausal women is an unresolved question, and needs further evaluation. Finally, we are in complete agreement with Stefanick regarding that for now; there is no magic bullet that can reduce the risks of major health problems related to estrogens and aging without introducing other potentially serious health concerns,[39] and that the common rules concerning drug therapy that apply for HT are that it should be prescribed for clear indications and monitored carefully, just as with other hormonal preparations, such as thyroid replacement therapy or insulin treatment.[40]

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