Review CPD

A pragmatic approach to the management of menopause

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Menopause is defined as 1 year of amenorrhea caused by declining ovarian reserve or as the onset of vasomotor symptoms in people with iatrogenic amenorrhea. It is preceded by perimenopause or the menopause transition, which can last for as long as 10 years. Although many treatments exist for menopausal symptoms, fears around the risks of menopausal hormone therapy and lack of knowledge regarding treatment options often impede patients from receiving treatment. In this review, we summarize the evidence for treating menopausal symptoms and discuss their risks and benefits to help guide clinicians to evaluate and treat patients during the menopausal transition (Box 1).

Key points

- Menopausal symptoms can occur for as long as 10 years before the last menstrual period and are associated with substantial morbidity and negative impacts on quality of life.
- Menopausal hormone therapy is indicated as first-line treatment of vasomotor symptoms, and is a safe treatment option for patients with no contraindications.
- Though less effective, nonhormonal treatments also exist to treat vasomotor symptoms and sleep disturbances.
- It is critical that clinicians inquire about symptoms during the menopause transition and discuss treatment options with their patients.

What is the prevalence and impact of menopausal symptoms?

The median age of menopause is 51 years, which has remained consistent over the last century, despite a trend toward an earlier age of menarche.[1,2] "Symptoms of menopause often start during the perimenopausal period, even as early as 10 years before the last menstrual period.[1,3] Globally, 1.0%–3.7% of women experience premature ovarian insufficiency, which leads to menopause before age 40 years and has a variety of causes, including chromosomal abnormalities, autoimmune processes, cancer treatment, surgery or idiopathic etiologies.[4]

Menopausal symptoms are variable and reflect a complex interaction between biological, psychological and social factors. Vasomotor symptoms (e.g., hot flashes, night sweats) are the most commonly reported and may affect as many as 80% of women.[5] Most vasomotor symptoms persist for fewer than 7 years after the final menstrual period; however, 25% of women may experience flushing for as long as 10 years, and 10% have these symptoms for more than 10 years.[6] In addition, vasomotor symptoms have been shown to independently predict increased cardiovascular risk, bone loss and high bone turnover.[7,8]

A higher burden of menopausal symptoms is associated with decreased mental and physical quality of life.[9] The transition into menopause, irrespective of symptoms, has also been associated with decreased health-related quality of life.[10] Symptoms can substantially affect work productivity, as well as health care use and costs.[9,11,12]

Box 1: Evidence used in this review

We searched PubMed from inception until April 2022 using the term "menopause" with keywords "symptoms," "diagnosis" and "treatment." We also reviewed relevant articles from the reference lists of selected articles. Selected articles included a combination of systematic reviews, practice guidelines, randomized controlled trials and cohort studies.

How is menopause diagnosed?

For people older than 45 years who have symptoms of menopause or amenorrhea, a work-up with laboratory tests and imaging is not indicated unless symptoms are suggestive of an alternative diagnosis. Pregnancy should be ruled out among sexually active patients who are not using contraception.

For patients younger than 45 years who present with irregular or absent menstrual cycles, clinicians should order follicle-stimulating hormone (FSH) levels, although FSH levels vary considerably during perimenopause.[13] Endocrine disorders should be ruled out as causes of secondary amenorrhea (e.g., hyperprolactinemia, hypothyroidism), as well as pregnancy (Table 1). For patients younger than 40 years who present with irregular cycles and menopausal symptoms, clinicians should conduct a complete work-up for secondary amenorrhea, including a FSH and serum estradiol.

Table 1: Investigations for secondary amenorrhea when indicated for patients younger than 45 years

Differential diagnosis	Diagnostic test
Premature ovarian insufficiency or early menopause	FSH, estradiol
Hyperprolactinemia	Serum prolactin
Pregnancy	β-hCG
Hypo- or hyperthyroidism	TSH
Polycystic ovary syndrome	Clinical diagnosis (i.e., Rotterdam criteria), with or without total serum testosterone

Note: FSH = follicle-stimulating hormone, hCG = human chorionic gonadotropin, TSH = thyroid-stimulating hormone.

For patients with vasomotor symptoms that are atypical, more frequent than would be expected or associated with other symptoms not usual in menopause, alternative diagnoses should be considered — such as carcinoid syndrome, pheochromocytoma, and hematologic or solid organ malignant diseases — and investigated accordingly (Table 2).

How should troubling symptoms be treated?

Menopausal hormonal therapy

Several international societies, including the Society of Obstetricians and Gynaecologists of Canada and the North American Menopause Society, recommend menopausal hormone therapy as the first-line treatment for vasomotor symptoms for both menopausal and perimenopausal patients.[14,15] The estrogen component of menopausal hormone therapy reduces bothersome menopausal symptoms, while the progestin protects the endometrium from hyperplasia and reduces the risk of endometrial cancer. Treatment with combined estrogen and progestin regimens (or estrogen alone, in patients who have had a hysterectomy) reduces the frequency and severity of hot flashes and night sweats by around 75%.[16] In Canada, systemic estrogens are available in oral form, or as a transdermal patch or gel; vaginal formulations exist in the form of creams, vaginal tablets or an insertable ring. Transdermal estrogen formulations bypass the first-pass effect of the liver and may be safer than other formulations with regard to stroke and clot risk.[14] Progestins are available as both synthetic progestins and micronized progesterone, and come in the form of oral pills, transdermal systems (in combination with estrogen) and an intrauterine device (Table 3).

Newer, single-dose combination treatments like tissue selective estrogen complexes (TSECs; e.g., conjugated estrogen and bazodoxifene) and selective tissue estrogen activity regulators (e.g., tibolone) can also be used as first-line treatments in place of traditional combination estrogen–progestin products. Tibolone carries similar risks to standard menopausal hormone therapy.[17] Although TSECs have similar adverse effects as menopausal hormone therapy, they are associated with less break-through bleeding and mastalgia; however, they have been unavailable in Canada since 2020 because of a packaging problem that has recently been resolved.

In the absence of contraindications, menopausal hormone therapy is the treatment of choice for patients within 10 years of their final menstrual period or, if this is unknown, younger than 60 years (Table 4).[14,16] Standard doses of menopausal hormone therapy for patients of average menopausal age are included in Table 3; doses for patients with premature ovarian insufficiency should be higher.[18] Duration of treatment after starting menopausal hormone therapy is no longer limited to 5 years, but rather is individualized, where the safest regimen is used at the appropriate doses to control symptoms.[15] For patients with premature ovarian insufficiency, hormone replacement should continue until the average age of menopause, irrespective of symptom burden and in absence of contraindications.

In Canada, no product for testosterone treatment has been approved or recommended for menopausal symptoms, but the International Menopause Society has a position statement regarding the off-label treatment of menopausal hypoactive sexual desire.[19]

Nonhormonal therapies

Although less effective than menopausal hormone therapy,[17] nonhormonal options should be considered if menopausal hormone therapy is not appropriate because of contraindications or patient preference.[14] Options include certain selective serotonin reuptake inhibitors (SSRIs), serotonin–norepinephrine reuptake inhibitors (SNRIs), gabapentinoids, clonidine and oxybutynin (Table 5). Gabapentionoids are particularly useful when taken at night to help alleviate nocturnal symptoms. A newer class, still

Table 2: Red flags and secondary work-up to consider for menopausal patients with vasomotor symptoms

Symptom	Differential diagnosis	Secondary work-up
B symptoms — night sweats accompanied by weight loss and fever	Malignancy (solid or hematological)	Appropriate work-up for malignant disease
Worsening VMS, remote from menopause transition	Coronary artery disease	Cardiac testing, as indicated (e.g., stress test, stress echo)
VMS with skin flushing, diarrhea or shortness of breath	Carcinoid syndrome	24-hour urine collection for 5-HIAA
Episodic headache, hypertension and palpitations	Pheochromocytoma	24-hour urine collection for total metanephrines

Note: 5-HIAA = 5-hydroxyindoleacetic acid, VMS = vasomotor symptoms.

awaiting approval, is the neurokinin-3 receptor antagonist, which acts to stabilize the temperature control centre in the hypothalamus.[20] Although some herbal supplements have been associated with improvement in menopausal symptoms, a review of nonpharmacologic treatments is beyond the scope of this article; the topic was recently reviewed in a menopause practice guideline by the Society of Obstetricians and Gynecologists of Canada.[14]

What are the benefits and risks of menopausal hormone therapy?

Benefits

Menopausal hormone therapy can improve vasomotor symptoms by as much as 90% in patients with moderate-to-severe hot flushes.[21] It also improves sleep quality[22] and mood disturbances.[23,24] Although systemic menopausal hormone therapy may also alleviate genitourinary syndrome of menopause, patients being treated primarily for this issue can be treated with lubricants, moisturizers, vaginal estrogens or oral selective estrogen receptor modulators alone.

Despite early concerns of an increased risk of cardiovascular events with menopausal hormone therapy after the Women's Health Initiative (WHI) trial,[25] increasing evidence shows a possible reduction in coronary artery disease (CAD) with menopausal hormone therapy among younger menopausal patients, specifically those who start menopausal hormone therapy before age 60 years or within 10 years of menopause.[26–30] Data from both randomized controlled trials (RCTs) and observational studies consistently show that menopausal hormone therapy is associated with a reduction in CAD events among these patients; menopausal hormone therapy should therefore be preferentially started during these time windows.[29] A reduction in overall mortality among patients who begin menopausal hormone therapy before age 60 years has also been reported.[27,31]

Table 3: Systemic menopausal hormone therapy products available in Canada

Generic name	Dosage	Relative cost per year, before pharmacy dispensing fees*†
Conjugated estrogens	0.3–0.625 mg once daily	+
17-β-estradiol (micronized)	0.5–1 mg once daily	+
Transdermal patch		
Twice weekly 17-β-estradiol patches	25–50 µg twice weekly	++
Transdermal gel		
17-β-estradiol gel	For 0.06% gel, 0.75 mg estradiol per 1.25 g metered dose (1 actuation). 1–2 metered doses/actuation daily	++
Progestins		
Oral		
Medroxyprogesterone	2.5 mg daily for continuous regimen or 5 mg daily for 12–14 d/mo	+
Progesterone (micronized)	100 mg daily for continuous regimen or 200 mg daily for 12–14 d/mo for cyclic regimen	+
Intrauterine		
Levonorgestrel intrauterine system‡	52 mg per intrauterine system for 5 years	+
Combination hormone therapy preparations		
Oral		
17-β-estradiol and NETA	1 mg 17-β-estradiol and 0.5 mg NETA once daily	+++
	0.5 mg 17-β-estradiol and 0.1 mg NETA once daily	+++
17-β-estradiol and DRSP	1 mg 17-β-estradiol and 1 mg DRSP once daily	++
Transdermal patch		
17-β-estradiol and NETA	50 µg 17-β-estradiol and 140 mg NETA patch twice weekly	++
	50 µg 17-β-estradiol and 250 mg NETA patch twice weekly	++
TSEC		
Conjugated estrogen and bazedoxifene	0.45 mg conjugated estrogen and 20 mg bazedoxifene once daily	+++
Synthetic steroid		
Tibolone	2.5 mg once daily	+++

Note: DRSP = drospirenone, NETA = norethindrone acetate, TSEC = tissue selective estrogen complex.
*Available from www.rxfiles.ca.
†Range of costs: + = < $300, ++ = $301–1000, +++ = > $1001.
‡Not approved for menopausal hormone therapy by Health Canada.

Table 4: Contraindications to systemic menopausal hormone therapy[14]

Hormone therapy	Contraindication
Estrogen	Undiagnosed abnormal vaginal bleeding
	Known, suspected or history of breast cancer
	Known, suspected or history of estrogen-dependent cancers (i.e., endometrial, ovarian)
	Active or history of coronary artery disease
	Active or history of venous thromboembolism
	Active or history of stroke
	Known thrombophilia
	Active liver disease (e.g., with abnormal liver function tests, cirrhosis)
Progestin	Undiagnosed abnormal vaginal bleeding
	Current or history of breast cancer

Reproduced with permission (Yuksel et al., 2021).[14]

Table 5: Nonhormonal menopausal treatments and suggested doses[14]

Type	Starting dose
SNRIs	
Venlafaxine	37.5–75 mg oral daily
Desvenlafaxine	100–150 mg oral daily
SSRIs	
Paroxetine	10–20 mg oral daily
Citalopram	10–20 mg oral daily
Escitalopram	10–20 mg oral daily
Gabapentinoids	
Gabapentin	100–300 mg oral at bedtime
Pregabalin	150–300 mg oral twice daily
Clonidine	0.05 mg oral twice daily
Oxybutynin	
Oxybutynin immediate release	2.5–5 mg oral twice daily
Oxybutynin XL	15 mg daily

Note: SNRI = serotonin–norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor.
Reproduced with permission (Yuksel et al., 2021).[14]

The metabolic benefits of menopausal hormone therapy include an improvement in lipid profile (increase in high-density lipoprotein, decrease in low-density lipoprotein, decrease in lipoprotein [a]), although oral estrogen may also increase triglyceride levels.[32] Some studies suggest an improvement in insulin sensitivity and, perhaps, a reduction in risk of diabetes.[33–35] For both lipid and insulin sensitivity, the benefits are seen primarily with oral estrogen therapy rather than transdermal formulations, given their hepatic first-pass effects.

Menopausal hormone therapy has been consistently associated with a reduction in the incidence of osteoporosis-related fractures.[25,36,37] The WHI study provided the best evidence on fracture risk reduction with menopausal hormone therapy, reporting a 34% reduction in hip fractures, a 34% reduction in vertebral fractures and a 23% reduction in other osteoporotic fractures among women who took hormone therapy compared with those who did not.[25] Although menopausal hormone therapy is not recommended by most osteoporosis guidelines as a primary treatment, it should be considered as a second-line treatment in symptomatic menopausal patients.[38]

Risks

Although many RCTs and observational studies have shown an increased risk of breast cancer with menopausal hormone therapy, these findings need to be interpreted carefully in the context of the individual patient. The WHI first reported that patients treated with combined menopausal hormone therapy had an increased risk of invasive breast cancer (hazard ratio 1.2).[39] However, the attributable risk is much lower among people aged 50–59 years or among those who start treatment within the first 10 years of menopause, for whom the additional risk of breast cancer is estimated at 3 additional cases for every 1000 women who use combined menopausal hormone therapy for 5 years.[40] In the WHI 20-year follow-up study, patients on conjugated estrogen alone showed a lower risk of breast cancer than those on placebo. Other studies also showed a lower risk of breast cancer among those on estrogen alone, compared with those on combined menopausal hormone therapy,[41,42] with synthetic progestins conferring a higher risk of breast cancer than micronized progesterone.[43] In patients with additional risk factors for breast cancer (e.g., family history, obesity, alcohol intake), the lowest effective dose of micronized progesterone or no progestin should be considered, if appropriate (i.e., TSEC or estrogen alone).

Although early RCT data suggested an increased risk of ischemic stroke among patients on menopausal hormone therapy (odds ratio 1.29), more recent data suggest that this risk is primarily among older patients (aged > 60 yr) who start menopausal hormone therapy after the 10 years following the onset of menopause.[44] For those younger than 60 years, the absolute risk of stroke from standard dose hormone therapy is about 2 additional strokes per 10 000 person-years of use. With regard to venous thromboembolic events, the WHI reported a twofold increased risk with hormone therapy, with the risk highest in the first year of use and with higher doses.[25] The reported absolute risk was 2–10 cases per 1000 users with short-term use (< 2 yr) and up to 28 cases per 1000 users with long-term use (> 7 yr).[45] Most recent studies show a lower risk of venous thromboembolic events with transdermal estrogen formulations compared with oral treatments.[46–48]

What are the considerations for starting menopausal hormone therapy?

For average-aged menopausal or perimenopausal patients with no contraindications for menopausal hormone therapy and no specific individual risk factors, no specific hormone regimen is preferred for menopause management. When starting a patient

on menopausal hormone therapy, clinicians should consider the patient's individual risk of disease (e.g., breast cancer, venous thrombolic events, stroke), preferred mode of delivery (oral v. transdermal, combination v. separate dosing), need for uterine protection and cost. Patients with risk factors for specific diseases like breast cancer should be offered an individualized regimen (e.g., the TSEC, conjugated estrogen alone, combination therapy with cyclic progesterone). Similarly, a patient at risk for venous thromboembolic events should be offered low-dose transdermal therapy.

Common adverse effects of menopausal hormone therapy include vaginal bleeding, mastalgia and headache. Unexpected vaginal bleeding is the most common adverse event with menopausal hormone therapy. Investigations for endometrial hyperplasia or cancer should be performed (i.e., ultrasonography, endometrial sampling) if the bleeding persists beyond 4–6 months, or in a patient with risk factors for endometrial cancer. It is not necessary to cease use of menopausal hormone therapy while investigations are ongoing. Options for decreasing unexpected vaginal bleeding include sequential progestin dosing (i.e., 12–14 days of the month); use of a levonorgestrel-releasing intrauterine system, tibolone or the TSEC (when available); or, in rare cases, hysterectomy. Evaluation of the endometrium with ultrasonography and histologic sampling, and titration of the dose of estrogen or progestin based on thickness and histologic phase, can be performed with or without referral to a gynecologist based on the comfort of the managing physician.

Mastalgia is a common estrogenic adverse effect and can raise concerns regarding breast cancer. It will usually improve over the first 3–4 months of treatment. Approaches to managing mastalgia include minimizing estrogen to the lowest effective dose or using conjugated estrogens, cyclic progestin dosing, tibolone or the TSEC (when available).[49]

Migraine is not a contraindication to the use of systemic menopausal hormone therapy. Migraine symptoms can be improved for some patients by using regular, continuous dosing of both estrogen and progesterone. For patients with contraindications to menopausal hormone therapy, escitalopram and venlafaxine have evidence both for improvement of vasomotor symptoms and migraine suppression.[50]

Box 2: Unanswered questions

- What is the optimal duration of treatment for menopausal hormone therapy?
- Are any hormonal formulations superior for either cardiovascular or bone protection?
- What are the optimal hormonal formulations to minimize risk from menopausal hormone therapy with regards to breast cancer and venous thromboembolic events?
- Will newer nonhormonal agents that act directly on brain receptors offer cardiovascular or bone protection?
- What is the work-up for vasomotor symptoms that are suspected to be nonmenopausal in etiology?
- What is the evidence for nonpharmacologic and lifestyle approaches to menopause management?

Conclusion

Menopause and perimenopause can be associated with distressing symptoms and reduced quality of life. Menopausal hormone therapy is the first-line treatment for vasomotor symptoms in the absence of contraindications. Patients with contraindications to estrogen and progestin therapy can be offered nonhormonal alternatives. Choice of menopause treatments depends on symptoms, patient preference, risk factors, absolute contraindications, availability and costs. Complex patients should be referred to specialists. Important clinical questions remain unanswered and should be tackled by future research (Box 2).

References

1. Bruce D, Rymer J. Symptoms of the menopause. *Best Pract Res Clin Obstet Gynaecol* 2009;23:25-32.
2. Palacios S, Henderson V, Siseles N, et al. Age of menopause and impact of climacteric symptoms by geographical region. *Climacteric* 2010;13:419-28.
3. Santoro N, Roeca C, Peters BA, et al. The menopause transition: signs, symptoms, and management options. *J Clin Endocrinol Metab* 2021;106:1-15.
4. European Society for Human Reproduction and Embryology (ESHRE) Guideline Group on POI; Webber L, Davies M, Anderson R, et al. management of women with premature ovarian insufficiency. *Hum Reprod* 2016;31:926-37.
5. El Khoudary SR, Greendale G, Crawford SL, et al. The menopause transition and women's health at midlife: a progress report from the Study of Women's Health Across the Nation (SWAN). *Menopause* 2019;26:1213-27.
6. Utian WH. Psychosocial and socioeconomic burden of vasomotor symptoms in menopause: a comprehensive review. *Health Qual Life Outcomes* 2005;3:47.
7. Avis NE, Crawford SL, Greendale G, et al. Duration of menopausal vasomotor symptoms over the menopause transition. *JAMA Intern Med* 2015;175:531-9.
8. Thurston RC, Aslanidou Vlachos HE, Derby CA, et al. Menopausal vasomotor symptoms and risk of incident cardiovascular disease events in SWAN. *J Am Heart Assoc* 2021;10:e017416.
9. Whiteley J, daCosta DiBonaventura M, Wagner J-S, et al. The impact of menopausal symptoms on quality of life, productivity, and economic outcomes. *J Womens Health (Larchmt)* 2013;22:983-90.
10. Hess R, Thurston RC, Hays RD, et al. The impact of menopause on health-related quality of life: results from the STRIDE longitudinal study. *Qual Life Res* 2012;21:535-44.
11. Kjerulff KH, Frick KD, Rhoades JA, et al. The cost of being a woman: a national study of health care utilization and expenditures for female-specific conditions. *Womens Health Issues* 2007;17:13-21.
12. Kleinman NL, Rohrbacker NJ, Bushmakin AG, et al. Direct and indirect costs of women diagnosed with menopause symptoms. *J Occup Environ Med* 2013;55:465-70.
13. Randolph JF Jr, Crawford S, Dennerstein L, et al. The value of follicle-stimulating hormone concentration and clinical findings as markers of the late menopausal transition. *J Clin Endocrinol Metab* 2006;91:3034-40.
14. Yuksel N, Evaniuk D, Huang L, et al. Guideline No. 422a: Menopause: vasomotor symptoms, prescription therapeutic agents, complementary and alternative medicine, nutrition, and lifestyle. *J Obstet Gynaecol Can* 2021;43:1188-204.e1.
15. "The 2022 Hormone Therapy Position Statement of The North American Menopause Society" Advisory Panel. The 2022 hormone therapy position statement of The North American Menopause Society. *Menopause* 2022;29:767-94.
16. Maclennan AH, Broadbent JL, Lester S, et al. Oral oestrogen and combined oestrogen/progestogen therapy versus placebo for hot flushes. *Cochrane Database Syst Rev* 2004;(4):CD002978.
17. Formoso G, Perrone E, Maltoni S, et al. Short-term and long-term effects of tibolone in postmenopausal women. *Cochrane Database Syst Rev* 2016;(10):CD008536.
18. Panay N, Anderson RA, Nappi RE, et al. Premature ovarian insufficiency: an International Menopause Society White Paper. *Climacteric* 2020;23:426-46.
19. Davis SR, Baber R, Panay N, et al. Global Consensus Position Statement on the use of testosterone therapy for women. *J Clin Endocrinol Metab* 2019;104:4660-6.

20. Depypere H, Lademacher C, Siddiqui E, et al. Fezolinetant in the treatment of vasomotor symptoms associated with menopause. *Expert Opin Investig Drugs* 2021;30:681-94.
21. Notelovitz M, Lenihan JP, McDermott M, et al. Initial 17beta-estradiol dose for treating vasomotor symptoms. *Obstet Gynecol* 2000;95:726-31.
22. Cintron D, Lipford M, Larrea-Mantilla L, et al. Efficacy of menopausal hormone therapy on sleep quality: systematic review and meta-analysis. *Endocrine* 2017;55:702-11.
23. Gordon JL, Rubinow DR, Eisenlohr-Moul TA, et al. Efficacy of transdermal estradiol and micronized progesterone in the prevention of depressive symptoms in the menopause transition: a randomized clinical trial. *JAMA Psychiatry* 2018;75:149-57.
24. Gleason CE, Dowling NM, Wharton W, et al. Effects of hormone therapy on cognition and mood in recently postmenopausal women: findings from the randomized, controlled KEEPS-Cognitive and Affective Study. *PLoS Med* 2015;12: e1001833; discussion e1001833.
25. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002;288:321-33.
26. Salpeter SR, Walsh JM, Greyber E, et al. Brief report: Coronary heart disease events associated with hormone therapy in younger and older women. A meta-analysis. *J Gen Intern Med* 2006;21:363-6.
27. Rossouw JE, Prentice RL, Manson JE, et al. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. *JAMA* 2007;297:1465-77.
28. Schierbeck LL, Rejnmark L, Tofteng CL, et al. Effect of hormone replacement therapy on cardiovascular events in recently postmenopausal women: randomised trial. *BMJ* 2012;345:e6409.
29. Nudy M, Chinchilli VM, Foy AJ. A systematic review and meta-regression analysis to examine the 'timing hypothesis' of hormone replacement therapy on mortality, coronary heart disease, and stroke. *Int J Cardiol Heart Vasc* 2019;22:123-31.
30. Hodis HN, Collins P, Mack WJ, et al. The timing hypothesis for coronary heart disease prevention with hormone therapy: past, present and future in perspective. *Climacteric* 2012;15:217-28.
31. Salpeter SR, Walsh JM, Greyber E, et al. Mortality associated with hormone replacement therapy in younger and older women: a meta-analysis. *J Gen Intern Med* 2004;19:791-804.
32. Walsh BW, Schiff I, Rosner B, et al. Effects of postmenopausal estrogen replacement on the concentrations and metabolism of plasma lipoproteins. *N Engl J Med* 1991;325:1196-204.
33. Mauvais-Jarvis F, Clegg DJ, Hevener AL. The role of estrogens in control of energy balance and glucose homeostasis. *Endocr Rev* 2013;34:309-38.
34. Salpeter SR, Walsh JM, Ormiston TM, et al. Meta-analysis: effect of hormone-replacement therapy on components of the metabolic syndrome in postmenopausal women. *Diabetes Obes Metab* 2006;8:538-54.
35. Manson JE, Rimm EB, Colditz GA, et al. A prospective study of postmenopausal estrogen therapy and subsequent incidence of non-insulin-dependent diabetes mellitus. *Ann Epidemiol* 1992;2:665-73.
36. Gambacciani M, Levancini M. Hormone replacement therapy and the prevention of postmenopausal osteoporosis. *Prz Menopauzalny* 2014;13:213-20.
37. Torgerson DJ, Bell-Syer SE. Hormone replacement therapy and prevention of vertebral fractures: a meta-analysis of randomised trials. *BMC Musculoskelet Disord* 2001;2:7. doi: 10.1186/1471-2474-2-7. [Epub ahead of print 2001 Nov. 6].
38. Eastell R, Rosen CJ, Black DM, et al. Pharmacological management of osteoporosis in postmenopausal women: an Endocrine Society* clinical practice guideline. *J Clin Endocrinol Metab* 2019;104:1595-622.
39. Chlebowski RT, Hendrix SL, Langer RD, et al. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: the Women's Health Initiative Randomized Trial. *JAMA* 2003;289:3243-53.
40. Stuenkel CA, Davis SR, Gompel A, et al. Treatment of symptoms of the menopause: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2015;100:3975-4011.
41. Schairer C, Lubin J, Troisi R, et al. Menopausal estrogen and estrogen-progestin replacement therapy and breast cancer risk. *JAMA* 2000;283:485-91.
42. Ross RK, Paganini-Hill A, Wan PC, et al. Effect of hormone replacement therapy on breast cancer risk: estrogen versus estrogen plus progestin. *J Natl Cancer Inst* 2000;92:328-32.
43. Abenhaim HA, Suissa S, Azoulay L, et al. Menopausal hormone therapy formulation and breast cancer risk. *Obstet Gynecol* 2022;139:1103-10.
44. Carrasquilla GD, Frumento P, Berglund A, et al. Postmenopausal hormone therapy and risk of stroke: A pooled analysis of data from population-based cohort studies. *PLoS Med* 2017;14:e1002445.
45. Marjoribanks J, Farquhar CM, Roberts H, et al. Cochrane corner: long-term hormone therapy for perimenopausal and postmenopausal women. *Heart* 2018; 104:93-5.
46. Hodis HN, Mack WJ. Menopausal hormone replacement therapy and reduction of all-cause mortality and cardiovascular disease: It is about time and timing. *Cancer J* 2022;28:208-23.
47. Harman SM, Black DM, Naftolin F, et al. Arterial imaging outcomes and cardiovascular risk factors in recently menopausal women: a randomized trial. *Ann Intern Med* 2014;161:249-60.
48. Canonico M, Oger E, Plu-Bureau G, et al. Hormone therapy and venous thromboembolism among postmenopausal women: impact of the route of estrogen administration and progestogens: the ESTHER study. *Circulation* 2007;115: 840-5.
49. Fornili M, Perduca V, Fournier A, et al. Association between menopausal hormone therapy, mammographic density and breast cancer risk: results from the E3N cohort study. *Breast Cancer Res* 2021;23:47. doi: 10.1186/s13058-021-01425-8.
50. Tarlaci S. Escitalopram and venlafaxine for the prophylaxis of migraine headache without mood disorders. *Clin Neuropharmacol* 2009;32:254-8.

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