

# DOES HORMONE REPLACEMENT THERAPY BENEFIT POST-MENOPAUSAL WOMEN? – A SCOPING REVIEW

VINODKUMAR MUGADA<sup>A,B,D-F</sup>

• ORCID: 0000-0002-9364-9874

RAJ KIRAN KOLAKOTA<sup>E,F</sup>

• ORCID: 0000-0001-9998-3059

SUJANA BHARGAVI JADDA<sup>B,E,F</sup>

• ORCID: 0000-0002-0367-2799

URMILA KOTAPADU<sup>B,E,F</sup>

• ORCID: 0000-0001-7687-903X

MOUNIKA VEESAM<sup>B,E,F</sup>

• ORCID: 0000-0002-0031-6342

Department of Pharmacy Practice,  
Vignan Institute of Pharmaceutical Technology,  
Duvvada, AP, India

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## ABSTRACT

Post-menopausal women experience symptoms such as irregular periods, lower fertility, vaginal dryness, hot flashes and night sweats. Hormone replacement therapy (HRT) relieves menopausal symptoms. The aim of this review was to assess the benefits and risks of HRT in post-menopausal women. A scoping review was conducted for original peer-reviewed English language papers using the electronic databases of PUBMED, JAMA, BMC and TRIP. The papers were subjected to a three-stage screening process. The type of study, year of study, age, participants, type of therapy and the aim of the study defined the inclusion and exclusion criteria. HRT was associated with reduced risk and prevalence of end-stage kidney disease, gastric esophageal reflux disease (GORD) symptoms, periodontal disease and associated with the increased risk of overall cancers. The benefits of HRT depend on the duration of therapy, formulation, route of administration, time of initiating therapy (age <60 years) and type of therapy. Post-menopausal symptomatic women mostly benefited with hormone replacement therapy. To reduce risks of adverse events, HRT should be initiated with appropriate monitoring.

**KEYWORDS:** hormone replacement therapy, benefits, risks, estrogen, progesterone

## BACKGROUND

Women between the ages of 47 and 53 years undergo an important life-transitioning phase called menopause. The symptoms of menopause include irregular periods, lower fertility, vaginal dryness, hot flashes, night sweats, disturbed sleep, urinary problems, emotional changes, problems focusing and learning, and other symptoms [1-3]. Recent experimental and clinical studies have indicated that the effects of HRT depend on the estrogen and progesterone formulation, dosage, mode of administration, patient's age, associated diseases, and duration of treatment [4, 5]. Several studies reported that mortality from all causes was lower in HRT users than in non-users [6, 7]. The purpose of this review was to evaluate whether postmenopausal women derive benefit from the HRT.

## METHODOLOGY

A scoping review was conducted to establish the nature and distribution of studies relevant to the research question. This review identified search four domains; postmenopausal women, 'Hormone replacement therapy, benefits and risks. The electronic databases of PUBMED, JAMA, BMC and TRIP were searched for original peer-reviewed English language papers from January 2008 to July 2018. The search period was chosen to include the time frame during which changes were made in excluding the association between benefits and risks while giving HRT to post-menopausal women. Eligibility criteria were framed to exclude irrelevant studies (tab. 1).

## Screening

An initial database search generated papers which were subjected to a three-stage screening process. In the

Table 1. Inclusion and exclusion criteria for articles

Parameter	Inclusion	Exclusion
Type of study	RCT, cohort studies, meta-analysis, systematic review	Cross-sectional study, case-control study
Year of study	2008-2018	Studies published before 2008
Aim	To assess the benefits and risks of HRT	Other aspects of hormone replacement therapy
Age (years)	45-65	<45 or >65
Type of article	Research	Abstracts, letters to the editor, short communications, case reports, case series
Participants	Post-menopausal women	Men, others
Type of therapy	Both mono and dual therapy	Nil
Language	English	Other

first stage, ineligible or duplicate titles were excluded during title screening, leaving the remaining titles which were subjected to abstract screening. The content of the abstracts was screened in the second stage to assess its applicability to the inclusion criteria. Where it was not possible to determine this from the level of detail in the abstract, the full paper was read and subjected to the inclusion and exclusion criteria. In the third stage, the full papers were screened for eligibility and the reference lists of the studies included were hand searched for additional papers, which resulted

in no further additions to the final number of papers determined relevant to the review.

## DISCUSSION

### Benefits of HRT

Table 2 depicts the benefits of HRT. HRT benefits postmenopausal women by reducing the risk of disease development. However, the benefits of the therapy depend on the duration of therapy, formulation, route of administration, time of initiating therapy (age <60 years) and type of therapy. Studies have suggested that transdermal estrogens might be safe with respect to thrombotic risk [8, 9]. The long-term use of estrogen with or without progestin was likely to be associated with a reduced risk of osteoporosis, improvement or stabilization of bone density [10, 11] and ischemic heart disease (IHD) [12]. Data from the largest randomized clinical trial (RCT) to assess the impact of HRT on cardiovascular (CV) outcomes, the Heart Estrogen Replacement Study (HERS) reported a null effect, with an increase in cardiovascular mortality in first 12 months and a reduction thereafter [13]. Estrogen and progestin reduces vasomotor symptoms, depression [14], cognitive functioning [16] and sleep disturbance [17, 18] and improves sexual functioning [15].

Carrasquilla et al [19] reported that the initiation of HRT 0±5 years after the onset of menopause, as compared to never used, was associated with a decreased

Table 2. Studies that reported benefits of hormone replacement therapy

Author & year of publication	Age of patients (in years)	Duration of therapy (in years)	Type of therapy	Benefits reported
Carrasquilla et al., 2017 [19]	Early HT initiation: Age at Baseline- 58.8 (54.8–60.5) Age at Menopausal Onset - 50.2 (48.0–53.0) Late HT initiation: Age at Baseline- 64.9 (60.0–70.2) Age at Menopausal Onset- 49.7 (46.0–52.0)	14.3	OE, CH	Initiation of HRT 0 ± 5 years after menopause onset, as compared to never used, was associated with a decreased risk of stroke and hemorrhagic stroke.
Simin et al., 2017 [20]	≥ 40	7	OE, CH, OP	HRT decreased the risk of gastrointestinal cancers.
Hale et al., 2015 [21]	---	---	---	HRT may play a role in primary CVD prevention if initiated within 10 years of menopause and at less than 60 years of age.
Gleason et al., 2015 [22]	OCEE - 52.8 (2.7) t-E- 52.6 (2.6)	CO- 2.85±0.49 MO- 2.76±0.57	OCEE, t-E	Extended therapy benefits for mood and vasomotor symptoms.
Close et al., 2012 [23]	OE - 52.6±7.23 CH- 50.9±5.54 OP- 49.1±5.44	5.4	OE, CH, OP	Use of monotherapy decreased GORD symptoms.
Evalt et al., 2011 [24]	ERT- 61.6±6.1	-	CEE	Estrogen administration was safe for short-term use and may result in an improvement of motor symptoms.
Canonica et al., 2010 [25]	54.0(4.3)	10.1	CEE, CH	Short-term use of transdermal estrogens alone or combined with progesterone could be an option in the management of postmenopausal symptoms.
Tarkkila et al., 2010 [26]	55.4±2.7	2	---	HRT use decreased periodontal infections.
Vickers et al., 2007 [27]	62.8	1	CEE, OP	Reduced risk of osteoporosis and ischemic heart disease.
Seed et al., 2000 [28]	58.2±6.7	3 months	OE, CH, OP, Androgen	HRT reduced CV risk factors in post-menopausal women with risk of CAD and also protected from osteoporosis.

OE - Only estrogen, OP - Only progestogen, CH - Combined hormone therapy, HT - Hormone therapy, CO - Cognitive outcomes, MO - Mood outcomes, OCEE - Oral conjugated equine estrogens, t-E - Transdermal estradiol, ERT - Estrogen replacement therapy, MPA - Medroxyprogesterone acetate.

risk of stroke and hemorrhagic stroke. Based on the type of therapy, if single conjugated equine estrogen (CEE) was used, late initiation was associated with a shorter stroke-free (fifth percentile differences [PD], -4.41 years; 95% CI -7.14 to -1.68) and hemorrhagic stroke-free (first PD, -9.51 years; 95% CI -12.77 to -6.24) period than never used. Simin et al [20] reported that HRT reduced the risk of gastrointestinal cancer. The risk of all gastrointestinal cancers was decreased (SIR Z 0.90, 95% CI: 0.86-0.94). Hale et al [21] reported that HRT may play a role in primary cardiovascular disease (CVD) prevention if initiated within 10 years of menopause and at less than 60 years of age. Gleason et al. reported that, in women with a mean age of 52.8 (2.7) using oral conjugated equine estrogen (OCEE) and those with a mean age of 52.6 (2.6) using transdermal estradiol (t-E), HRT improved mood and decreased vasomotor symptoms. Close et al [23] reported that there was an independent association between HRT and risk of GORD symptoms and that estrogen decreased the risk of GORD compared to progesterone. This association remained statistically significant for estrogen-only treatment (OR 1.49; 1.18-1.89). Evalt et al [24] reported that estrogen administration was safe for short-term use and may result in an improvement of motor symptoms in women with a mean age of 61.6±6.1years.

Canonico et al [25] reported that oral estrogen increased the risk of venous thromboembolism, especially during the first year of treatment, whereas transdermal estrogen did not. Tarkkila et al [26] reported that HRT use for a duration of 2 years decreased periodontal infections in women with a mean age of 55.4±2.7 years. Vickers et al [27] reported that long-term use of estrogen was likely to be associated with a reduced risk of osteoporosis and ischemic heart disease. Concomitant use of progesterone has been shown to protect against endometrial cancer. The drugs and doses given were conjugated equine estrogens 0.625 mg orally daily; conjugated equine estrogens plus medroxyprogesterone acetate 2.5/5.0 mg orally daily; matched placebo. Seed et al [28] reported that all HRT regimens lower low-density lipoprotein cholesterol and reduced cardiovascular risk factors in post-menopausal women with risk of coronary artery disease (CAD).

### Risks of HRT

Table 3 summarizes the risks of HRT. Some of the most serious adverse effects of postmenopausal HRT in the general population are venous thromboembolism (VTE) and breast, ovarian, and endometrial malignancy [29]. Studies have shown breast cancer and endometrial cancer risk is greater if therapy is

Table 3. Studies that reported risks of hormone replacement therapy

Author name & Year of publication	Mean age of patients (in years)	Duration of therapy (in years)	Type of therapy	Risks
Dumanski et al., 2017 [35]	---	---	---	Women with chronic kidney disease are at increased risk of VTE and cancer
Simin et al., 2017 [20]	40	7	OE, CH, OP	A slight increase in overall cancer risk among HRT users, mainly cancer of the female reproductive organs.
Gleason et al., 2015 [22]	OCEE - 52.8 (2.7) t-E- 52.6 (2.6)	CO- 2.85±0.49 M0- 2.76±0.57	OCEE, t-E	Risk of breast cancer is seen unless given in a low dose for a brief period
Chlebowski et al., 2015 [36]	CH- 63.2±7.1 CEE-63.6±7.3	CH/placebo- 5.6 CEE/placebo- 7.2	CEE, CH	Estrogen plus progestin was associated with greater breast cancer incidence and mortality.
Tranah et al., 2010 [37]	CU- 82.9±3.4 PU- 83.8±3.4	4 consecutive 24hrs period	CEE, CH, OP	Vascular side-effects of HRT may exceed its beneficial effects on sleep
Beral et al., 2015 [38]	-	PS- 6 RS- 4	CEE, CH	Increase in ovarian cancer risk.
Nordenvall et al., 2014 [39]	PU- 64 CU- 60	14	-	Use of HRT may increase the risk of cholecystectomy.
Farhat et al., 2013 [40]	64.3±6.8	5.6	CH	Women with lower dose E + P treatment were at greater risk of breast cancer.
Engel et al., 2011 [41]	53.8	11.5±4.4	-	Short duration, whatever the progesterone or route of administration, does not reduce the risk of fracture over the medium or long term.
Cravioto et al., 2011 [42]	47.4±7.4	2	CH	Risk of developing thrombosis
Vickers et al., 2007 [27]	62.8	1	CEE, OP	Increased risks of breast and endometrial cancer.
Cirillo et al., 2005 [43]	CH- 63.1±7.1 CEE- 63.4±7.2	CH- 5.6 CEE- 7.1	CH, CEE	Increase in risk of biliary tract disease among postmenopausal women using estrogen therapy.
Shumaker et al., 2004 [44]	-	CEE- 5.21±1.73 CH- 4.05±1.19	CH, CEE	Increased risk of dementia and MCI in the estrogen alone and estrogen plus progestin trials among women between 65 and 79 years of age.
Rossouw et al., 2002 [30]	63.2±7.1	5.2	CH	Overall health risks exceed benefits with the use of combined estrogen plus progestin and this regimen should not be initiated or continued for the prevention of CHD.
Nelson et al., 2002 [45]	CU- 69.3 PU- 70.9 COU- 70.7	10	CEE	Prolonged postmenopausal estrogen use provided incomplete protection against osteoporotic fractures and women having osteoporosis who are at high risk of fractures.

CU- Current users, PU- Past users, COU- Continuous users, CH- combined hormone therapy, CEE- conjugated equine estrogens, CHD chronic heart disease.

initiated around the time of menopause [29,30-31]. A systematic review based of 10 RCT's concluded that oral HRT in postmenopausal women increases the risk of stroke [32] and coronary heart disease [33]. Data from the Women's Health Initiative (WHI) showed that HRT increased the risk of myocardial infarction, breast cancer, stroke, and blood clots [30,34].

Dumanski et al [35] reported that women with chronic kidney disease are at increased risk of VTE and cancer, both adverse effects of postmenopausal hormone therapy. Simin et al [20] reported that HRT causes a slight increase in overall cancer rates, mainly due to an increased risk of cancer of female reproductive organs. Ovarian cancer ranks as the sixth most common cancer and the seventh major cause of cancer death among women. The risk for invasive breast, endometrial or ovarian cancer combined was increased for any HRT, particularly Estrogen-Progestin-HRT (SIR Z 1.31, 95% CI: 1.28-1.34) and relative risk (RR) of 1.24; 95% confidence interval [CI] 1.15–1.34) from cohort studies and a summary odds ratio [OR] of 1.19 (95% CI 1.02–1.40) from case-control studies compared to never used HRT. Gleason et al [22] reported that an increased risk of breast cancer in women taking CEE with a mean age of 52.8 (2.7) and in those taking t-E with a mean age of 52.6 (2.6) was seen unless HRT was given in a low dose for a brief period. Chlebowski et al [36] reported that, in patients given estrogen plus progesterone, the incidence of breast cancer was initially higher compared to placebo, but this difference in incidence decreased in about 2 years and that the increased risk of breast cancer associated with the use of estrogen plus progestin declined soon after discontinuation of combined hormone therapy. Tranah et al [37] reported that the vascular side-effects of HRT may exceed its beneficial effects on sleep in women with a mean age of 83.8±3.4. Beral et al [38] reported that HRT with either CH or CEE increases the risk of ovarian cancer. Nordenvall et al [39] stated that use of HRT may increase the risk of cholecystectomy. HR of cholecystectomy was 1.52 (95% CI, 1.33–1.74) among ever users of HRT compared with never users. The risk did not differ by current or past use (P = 0.38) or duration of use (P = 0.65), but it did differ by indication for use (P = 0.006). Women who used HRT for systemic symptoms had a higher risk of cholecystectomy than those who used it for localized symptoms (HR, 1.62; 95% CI, 1.41–1.87 vs. HR, 1.21; 95% CI, 0.97–1.50). Farhat et al [40] reported that women with a mean age of 64.3 (6.8) taking a lower dose of CH for a duration of 5.6 years were at greater risk of breast

cancer. Engel et al [41] reported that giving HRT for a short duration, whatever the progesterone or route of administration, might reduce the risk of fracture over the medium or long term in women with a mean age of 53.8 years. Cravioto et al [42] reported an increased risk of venous thrombosis in women with a mean age of 47.4 (7.4) taking CH. Vickers et al [27] reported that in women with a mean age of 62.8, taking CEE and OP resulted in increased risks of breast and endometrial cancer.

Cirillo et al [43] reported that estrogen therapy increased the risk of biliary tract disease among postmenopausal women. Women with a history of hysterectomy were randomized to 0.625mg/d of CEE or placebo. Women without hysterectomy were randomized to estrogen plus progestin (E+P), given as CEE plus 2.5mg/d of medroxyprogesterone acetate (MPA). Both trials showed a greater risk of any gallbladder disease or surgery with estrogen (CEE: HR, 1.67; 95% CI, 1.35-2.06; E+P: HR, 1.59; 95% CI, 1.28-1.97). Shumaker et al [44] reported that an increased risk for dementia and no effect on mild cognitive impairment (MCI) in women treated with CEE plus MPA. In the estrogen-alone trial, subjects received 1 daily tablet containing either 0.625 mg/d of CEE vs. matching placebo. In the estrogen plus progestin trial, subject received 1 daily tablet containing CEE (0.625 mg/d) plus MPA (2.5 mg/d) vs. matching placebos. HR for probable dementia was 1.76 (95% CI, 1.19-2.60; P=.005) and for MCI, HR was 1.77 (95% CI, 0.74-4.23; P=.20) in the estrogen-alone trial and 2.19 (95% CI, 1.25-3.84; P=.006) in the pooled trials. Rossouw et al [30] reported that the overall health risks exceed benefits from the use of combined estrogen plus progestin and this regimen should not be initiated or continued for the prevention of chronic heart disease (CHD). Nelson et al [45] reported that the prolonged use of estrogen in postmenopausal women with a mean age of 69.3 in current users, 70.9 in past users and 70.7 in continuous users, provided incomplete protection against osteoporotic fractures. Women with osteoporosis who are at a high risk for fractures.

## CONCLUSIONS

The benefits of HRT are based on the duration of therapy, the age of initiating therapy, route of administration, and type of therapy (mono/dual). Initiating HRT in post-menopausal women will not yield maximum number of beneficial outcomes, unless the above factors are taken into consideration and therapy planned the accordingly.

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#### Correspondence address:

Vinodkumar Mugada  
Assistant Professor  
Department of Pharmacy Practice  
Vignan Institute of Pharmaceutical Technology  
Phone: (+91) 7095197222  
E-mail: mugadavinodkumar18@gmail.com

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