TITLE: Oral Progesterone for the Treatment of Menopausal Symptoms: A Review of the Clinical Evidence

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CONTEXT AND POLICY ISSUES

Menopause is the cessation of menses caused by progressively reduced levels of estrogen production by the ovaries.[1] The decline in hormone production often begins when a woman is in her late thirties, with near-complete loss of production occurring in her mid-fifties.[1] Estrogen deficiency is associated with hot flashes, insomnia, night sweats, mood disturbances, and vaginal dryness and discomfort.[1] Although some menopausal women may be asymptomatic, the majority of women (80%) will experience a combination of these symptoms.[1]

Hormone replacement therapy (HRT) is used for the management and relief of menopausal symptoms. Estrogen preparations can be administered systemically via an oral or transdermal route.[2] However, unopposed estrogen therapy in postmenopausal women may increase the risk of hyperplasia and endometrial cancer due to stimulation of the endometrium lining.[3] As progesterone can protect the endometrium against the proliferative effects of estrogens, postmenopausal women with an intact uterus have been recommended to receive combined HRT with estrogens and progestagens (progesterone or synthetic progestins).[1,3]

Two orally administered progestagens are micronized progesterone (Prometrium), a natural, bio-identical hormone, and methoxyprogesterone acetate (MPA; Provera), a synthetic hormone. According to the Health Canada product monographs, Prometrium and Provera are indicated for women with an intact uterus as an adjunct to postmenopausal estrogen replacement therapy to oppose the effects of estrogen on the endometrium.[4,5] Prometrium is available as 100 mg capsules and the recommended dose is 200 mg daily for the last 14 days of estrogen treatment per cycle, with high doses administered for higher doses of estrogen.[5] Provera is available as 2.5 mg, 5 mg or 10 mg tablets and the recommended dose is 5 mg to 10 mg daily for the last 12 to 14 days of estrogen treatment per cycle, using the lowest dose required to protect the endometrium from estrogenic-hyperstimulation.[4]

Although combined estrogen and progestagen therapy may alleviate the risk of endometrial complications, there have been other risks associated with this HRT. The Women's Health

Initiative (WHI) conducted a large-scale randomized controlled trial (N = 16,608) comparing conjugated equine estrogens (0.625 mg/day) plus MPA (2.5 mg/day) therapy with placebo in postmenopausal women.[6] The study was terminated early due to an increased risk of invasive breast cancer, coronary heart disease, stroke, and pulmonary embolism in the HRT group.[7] As MPA is a synthetic hormone, there may be potential safety and efficacy benefits to using a bioidentical hormone such as micronized progesterone.[8] Further controlled trials are needed to delineate these differences more clearly.[8,9]

The purpose of this review is to examine the clinical efficacy of micronized progesterone and MPA, individually and comparatively, for the management of menopausal symptoms.

RESEARCH QUESTIONS

1. What is the clinical efficacy of micronized progesterone for the management of menopausal symptoms?

2. What is the clinical efficacy of medroxyprogesterone for the management of menopausal symptoms?

3. What is the comparative clinical efficacy of micronized progesterone versus medroxyprogesterone for the management of menopausal symptoms?

KEY FINDINGS

Conjugated equine estrogens plus medroxyprogesterone (MPA) did not increase the risk of developing atrial fibrillation, increased the risk of invasive breast cancer, and increased the incidence of deaths attributed to lung cancer compared to placebo in the Women's Health Initiative study. Women who used estrogen preparations containing MPA had a higher risk of venous thromboembolism in the Million Women Study. Another study found that the addition of MPA to oral estradiol in women with hot flashes increased the occurrence of supraventricular ectopic activity, which is associated with an increased risk of atrial fibrillation and stroke. One study found that micronized progesterone was effective for decreasing the frequency and severity of hot flashes and night sweats in healthy postmenopausal women when compared to placebo. There were no comparative studies of micronized progesterone versus MPA for the management of menopausal symptoms.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2014, Issue 3), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No methodological filters were applied to limit retrieval by publication type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2009 and March 28, 2014.

Selection Criteria and Methods

One reviewer screened the titles and abstracts of the retrieved publications and evaluated the full-text publications for the final article selection, according to selection criteria presented in Table 1.

Table 1: Selection Criteria

Population	Menopausal women
Intervention	Q1+Q3: Micronized progesterone (Prometrium) Q2: Medroxyprogesterone acetate (Provera)
Comparator	Q1+Q2: Placebo Q3: Medroxyprogesterone acetate (Provera)
Outcomes	Relief of menopausal symptoms, cardiovascular risk, adverse events.
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials (RCTs) and non-randomized studies.

Exclusion Criteria

Studies were excluded if they did not meet the selection criteria, were duplicate publications or had been included in a selected systematic review, or were published prior to 2009.

Critical Appraisal of Individual Studies

The quality of randomized controlled trials and non-randomized studies were evaluated using the Downs and Black instrument.[10] A numeric score was not calculated for each study. Instead, strengths and limitations of each study were summarized and described.

SUMMARY OF EVIDENCE

Quantity of Research Available

The literature search yielded 269 citations. Upon screening titles and abstracts, 253 citations were excluded and 16 potentially relevant articles were retrieved for full-text review. No addition potentially relevant reports were identified through grey literature searching. Of the 16 potentially relevant reports, 6 were included in this review. The study selection process is outlined in a PRISMA flowchart (Appendix 1). Three analyses of the Women's Health Initiative estrogen plus progestin RCT, two RCTs, and one report of the Million Women prospective cohort study met inclusion.

Summary of Study Characteristics

Details on study characteristics can be found in Appendix 2.

Study design and country of origin

The estrogen plus progestin component of the Women's Health Initiative (WHI) was a multicenter RCT conducted in US clinical centers that was stopped after a mean of 5.2 years of

follow-up when overall risks exceeded benefits for the main study outcomes.[11-13] The Million Women Study was a multicenter, prospective cohort study conducted in the UK to examine how various reproductive and lifestyle factors affect women's health.[14] One double-blind RCT was conducted in a Canadian hospital-based academic center.[15] One double-blind, double-dummy RCT was conducted in Finland.[16]

Patient population

The WHI study included 16,608 postmenopausal women with a mean age of 63.2 years who had not had a hysterectomy and with no prior history of breast cancer, or prior cancer within the last 10 years except nonmelanoma skin cancer.[11-13] The Million Women Study recruited over one million UK women with a mean age of 56.7 years.[14] Two RCTs included healthy, early postmenopausal women who had never used HRT.[15,16] One RCT included women who were 1 to 10 years since final menstruation with a mean age of approximately 55 years.[15] The other RCT included women who were 6 to 36 months since final menstruation with a mean age of 52.5 years.[16]

Interventions and comparators

The WHI study randomized women to receive a single tablet of conjugated equine estrogen (CEE) 0.625 mg and medroxyprogesterone (MPA) 2.5 mg daily, or an identical-appearing placebo tablet.[11-13] The Million Women Study administered a questionnaire that required the respondent to indicate current or prior HRT use.[14] Analyses were performed using women who used estrogen plus progestin therapies compared to women who had never used HRT.[14] Estrogen plus progestin therapies were also further subdivided into the type of progestin used, which included MPA.[14] One RCT compared oral micronized progesterone 300 mg once-daily to placebo.[15] One RCT compared a regimen of oral estradiol 2 mg with MPA 5 mg once-daily to oral estradiol alone and to placebo.[16]

Outcomes measured

The studies that analyzed the WHI study evaluated the incidence of atrial fibrillation,[11] breast cancer,[12] and lung cancer.[13] The study reporting findings from the Million Women Study evaluated the incidence of venous thromboembolism (VTE), which included deep vein thrombosis (DVT) or pulmonary embolism.[14] One RCT reported vasomotor symptom (VMS) frequency.[15] One RCT reported heart rate variability over a 24-hour period as determined by electrocardiogram (ECG) recordings.[16]

Summary of Critical Appraisal

The WHI study recruited a large, diverse population and used adequate randomization and blinding procedures.[11-13] In all of the included analyses of the WHI study, sensitivity analyses were performed to evaluate the robustness of the findings. The WHI study used breast cancer as a primary safety outcome,[12] but it was not powered to detect differences in the incidence of atrial fibrillation[11] or lung cancer.[13] Although the outcomes were clearly defined in the studies, the analyses of the WHI study were conducted post-hoc and may be subject to spurious findings.[11-13] In the breast cancer study, not all patients consented to longer-term follow-up, which may have affected the findings.[12]

The Million Women Study recruited a large sample size reflective of women in the UK, which provided adequate power for detecting differences in several outcomes.[14] As it was a population-based cohort study, there may have been errors in the reporting of HRT use. In the included study, the absolute numbers of patients on the various types of progestin therapies were not reported.

In the two double-blind RCTs conducted in healthy, postmenopausal women, the sample sizes were relatively small (n=133, 150) and the study durations were shorter (12 weeks and 6 months).[15,16] One RCT[15] performed an adequate power calculation to determine an appropriate sample size, while the other RCT did not describe their power calculation.[16] In addition, the recruitment of healthy, early postmenopausal women may limit the generalizability of results to women not meeting these characteristics. In one RCT, the majority of patients were aware of their assigned treatment as determined by a questionnaire at the end of the study.[15] In the other RCT, multiple comparisons were performed using subgroups with few patients and results should be interpreted with caution.[16]

Summary of Findings

What is the clinical efficacy of micronized progesterone for the management of menopausal symptoms?

One 16-week RCT conducted in Canada compared oral micronized progesterone (Prometrium) 300 mg with placebo for the treatment of hot flashes and night sweats.[15] This dose is higher than the Health Canada-recommended dose of 200 mg and it was administered as monotherapy instead of as an adjunct to estrogen therapy. The RCT found that both micronized progesterone and placebo decreased the frequency and severity of vasomotor symptoms (VMS), but this decrease was more pronounced in the micronized progesterone group. According to the study authors, the difference in decrease between the micronized progesterone and placebo groups was clinically important. Statistical significance was not determined in this study. Adherence to study medication was determined by pill counts and diary records, and was found to be high (83% of women took ≥ 80% of pills for ≥ 60 days). The majority of women (54% with progesterone; 69% with placebo), however, correctly identified their therapy assignment despite being blinded to treatment.

What is the clinical efficacy of medroxyprogesterone for the management of menopausal symptoms?

Three analyses of the WHI study were included in this review.[11-13] One study found that there was no statistically significant increase in the risk of developing atrial fibrillation in postmenopausal women with no prior hysterectomy assigned to therapy with conjugated equine estrogens and medroxyprogesterone acetate (MPA+CEE) compared to placebo throughout 5.6 years of follow-up.[11] Sensitivity analyses using various definitions of atrial fibrillation did not alter these results.

The analysis of breast cancer outcomes in the WHI study found that CEE+MPA increased the incidence of invasive breast cancer when compared to placebo though a mean follow-up time of 11.0 years.[12] These breast cancers were more commonly node-positive, and there were more deaths attributed to breast cancer (2.6 vs 1.3 per 10,000 women per year) and more deaths due to all causes following a diagnosis of breast cancer (5.3 vs 3.4 per 10,000 women per year) in

the MPA+CEE group compared to the placebo group. Subgroup analysis found significant interaction with prior use of estrogen plus progestin therapies (P=0.03).

The analysis of lung cancer in the WHI study found that that use of CEE+MPA did not increase the incidence of lung cancer when compared to placebo.[13] The use of CEE+MPA did significantly increase deaths from lung cancer (HR 1.71, 95% CI 1.16 to 2.52, P=0.01), particularly deaths from non-small cell lung cancer. Subgroup analyses by smoking status did not find any statistically significant differences in the risk of death from lung cancer in each group, but sample sizes were small. As lung cancer was not a predefined outcome in the WHI estrogen plus progestin study, results should be interpreted with caution.

The Million Women Study found that for users of oral estrogen plus progestin HRT, the use of preparations containing MPA was associated with a higher risk of venous thromboembolism (VTE) when compared to women who had never used HRT in the past (RR 2.67, 95% CI 2.25 to 3.17).[14] Preparations containing MPA were associated with a statistically significantly higher risk of VTE than preparations containing norethisterone or norgestrel.

One RCT found that the combination of oral estradiol and MPA in women with hot flashes may lead to an increased occurrence of supraventricular ectopic beats when compared to oral estradiol alone.[16] The sample sizes of these comparison groups were small (n=17), so findings may be spurious.

What is the comparative clinical efficacy of micronized progesterone versus medroxyprogesterone for the management of menopausal symptoms?

No evidence on the comparative clinical efficacy of micronized progesterone versus medroxyprogesterone for the management of menopausal symptoms was identified.

Limitations

Three studies included in this review were analyses of the WHI estrogen plus progestin study, which limits the actual amount of novel information in this review. In addition, some of these analyses were conducted using outcomes that were not predefined in the original study, which may results in spurious findings.

There was one study that examined the clinical efficacy of micronized progesterone for the management of menopausal symptoms. This study was conducted in a Canadian setting, but was limited by its short duration, small sample size, and unblinding during the study. In addition, this study was conducted in healthy, early postmenopausal women, which would limit the ability to generalize findings to women outside of this population. Micronized progesterone was not administered as an adjunct to estrogen in this study, despite of this being the recommended mode of administration in the Health Canada product monograph.

There were no comparative studies of micronized progesterone versus MPA for the management of menopausal symptoms. As the outcomes examined in the included studies were different, it is difficult to draw any comparisons of efficacy or safety between micronized progesterone and MPA.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

According to the Women's Health Initiative estrogen plus progestin study, conjugated equine estrogens plus MPA did not increase the risk of developing atrial fibrillation, increased the incidence of invasive breast cancer, and increased the incidence of deaths attributed to lung cancer compared to placebo. Only breast cancer was a pre-specified safety outcome in the WHI study. The Million Women Study conducted in the UK found that women who used HRT preparations containing estrogen and MPA had a higher risk of venous thromboembolism. Another study found that the addition of MPA to oral estradiol in women with hot flashes increased the occurrence of supraventricular ectopic activity, which is associated with an increased risk of atrial fibrillation and stroke.

One study found that micronized progesterone was effective for decreasing the frequency and severity of hot flashes and night sweats in healthy postmenopausal women when compared to placebo, but this study was limited by its small sample size and short duration. In addition, generalizability of results was limited by the lack of estrogen administration, as micronized progesterone (Prometrium) is to be used as an adjunct to estrogen replacement therapy according to the Health Canada product monograph.[5]

There were no comparative studies of micronized progesterone versus MPA for the management of menopausal symptoms. As the outcomes examined in the included studies were different, it is difficult to draw any comparisons of efficacy or safety between micronized progesterone and MPA.

Large-scale safety and efficacy data on micronized progesterone are lacking due to the earlier and more common use of progestins rather than progesterone and further research is needed.

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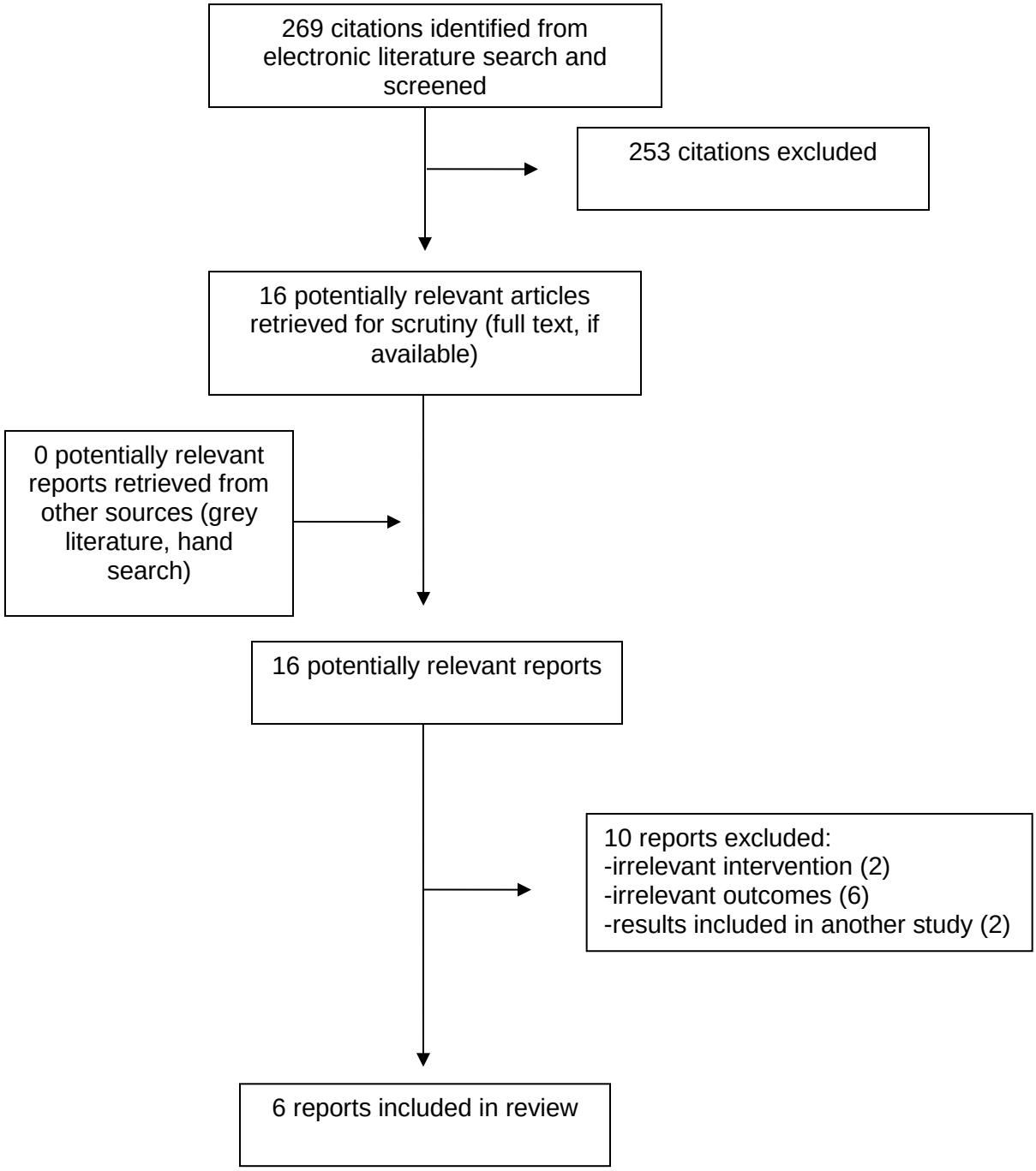
APPENDIX 1: Selection of Included Studies



APPENDIX 2: Study Characteristics

First Author, Publication Year, Country	Study Design and Length	Patient Characteristics	Intervention	Comparator	Clinical Outcomes Measured
Women's Health Initiative					
Perez[11] 2012 USA	RCT 5.6 years of follow-up (intervention phase)	16,608 postmenopausal women 50 to 79 years who had not had a hysterectomy; mean age 63.2 ± 7.1 years	CEE 0.625 mg/d + MPA 2.5 mg/d (n=8255 – no AF at BL)	Placebo (n=7873 – no AF at BL)	Incident AF (ECG and diagnosis codes from Medicare claims or hospitalization records)
Chlebowski[12] 2010 USA	RCT 11.0 (SD 2.7) years follow-up (intervention+ post-intervention phase)	16,608 postmenopausal women 50 to 79 years who had not had a hysterectomy and no prior breast cancer; mean age 63.2 ± 7.1 years	CEE 0.625 mg/d + MPA 2.5 mg/d (n=8506)	Placebo (n=8102)	Incidence of breast cancer (yearly mammograms and breast exams required during intervention, encouraged after intervention) – categorized by HER2 and HR status, deaths due to breast cancer
Chlebowski[13] 2009 USA	RCT 5.6 years intervention, 2.4 years additional follow-up	16,608 postmenopausal women 50 to 79 years who had not had a hysterectomy and no prior cancer within the last 10 years (except non-melanoma skin cancer); mean age 63.2 ± 7.1 years	CEE 0.625 mg/d + MPA 2.5 mg/d (n=8506)	Placebo (n=8102)	Incidence of lung cancer (overall, small cell and non-small cell), deaths due to lung cancer
Million Women Study					
Sweetland[14] 2012 UK	Multicenter, prospective cohort study Follow-up of 3.1 years per woman	1,058,259 postmenopausal women; mean age 56.7 ± 4.5 years – 36% current and 19% past users of HRT	Users of Estrogen + Progestin (n=196,358) -MPA subgroup	Never users of HRT (n=476,711)	Incidence of VTE (deep vein thrombosis or pulmonary embolism as hospital admission or cause of death)
Other Studies					
Hitchcock[15] 2012 Canada	Double-blind RCT 4 week run-in 12 week experimental phase	133 healthy postmenopausal community women 1 to 10 years since final menstruation seeking treatment for VMS with no HRT in past 6 months	Oral micronized progesterone (Prometrium) 300 mg/d (n=68 – 75 randomized) Mean age 55.5 ± 4.2 years	Placebo (n=46 – 58 randomized) Mean age 54.4 ± 4.6 years	VMS frequency, VMS severity, VMS score (night sweat frequency x night sweat severity + hot flash frequency x hot flash severity) – self-reported questionnaires

First Author, Publication Year, Country	Study Design and Length	Patient Characteristics	Intervention	Comparator	Clinical Outcomes Measured
Lantto[16] 2012 Finland	Double-blind, double-dummy RCT 6 months	150 healthy postmenopausal women 48 to 55 years, 6 to 36 months since menopause who have never used HRT; 72 women with hot flashes (mean age 52 ± 2 years); 78 women without hot flashes (mean age 53 ± 2 years)	Oral estradiol 2 mg/d + MPA 5 mg/d (n=37)	Oral estradiol 2 mg (n=38) Transdermal estradiol 1 mg (n=37) Placebo (n=38)	Heart rate variability over a 24 hour period (ECG recordings)

AF = atrial fibrillation; BL = baseline; CEE = conjugated equine estrogens; ECG = electrocardiogram; HF = hot flash; HR = hormone receptor; HRT = hormone replacement therapy; MPA = medroxyprogesterone acetate; RCT = randomized controlled trial; SD = standard deviation; VMS = vasomotor symptoms; WHI = Women's Health Initiative

APPENDIX 3: Summary of Critical Appraisal

First Author, Publication Year	Strengths	Limitations
Perez[11] 2012 WHI (atrial fibrillation)	• Large sample size with a diverse population • Adequate randomization and blinding methodologies (WHI) • Outcome definitions clearly defined • Sensitivity analyses were performed	• The WHI trial was not powered to detect differences in AF • It was unclear whether AF analyses were performed by blinded reviewers
Chlebowski[12] 2010 WHI (breast cancer)	• Large sample size with a diverse population • Adequate randomization and blinding methodologies (WHI) • Primary safety outcome was breast cancer • Sensitivity analyses were performed	• Not all participants consented to longer-term follow-up • There was no information on breast cancer therapies used
Chlebowski[13] 2009 WHI (lung cancer)	• Large sample size with a diverse population • Adequate randomization and blinding methodologies (WHI) • Sensitivity analyses were performed	• Lung cancer was not a predefined study outcome • The WHI trial was not powered to detect differences in lung cancer incidence • Post-hoc analysis
Sweetland[14] 2012 Million Women Study (venous thromboembolism)	• Large sample size • Subgroup analyses were performed	• No randomization or blinding • Absolute numbers of patients taking the various types of progestin therapies were not reported • Not all potential confounders were taken into account in the study
Hitchcock[15] 2012 (vasomotor symptoms)	• Method of randomization described • Outcomes clearly defined • Adherence to medication was measured	• Sample size was relatively small (n=133) • Trial duration was short (12 weeks) • This healthy population may not be representative of all women with menopause • ITT analysis was not used • The majority of patients were aware of their assigned treatment
Lantto[16] 2012 (heart rate variability)	• Outcomes clearly defined	• Method of randomization not described • Sample size was relatively small (n=150), particularly when groups were divided according to treatment and hot flash status • Treatment duration was relatively short (6 months) • Multiple comparisons were performed using small subgroups • This healthy population may not be representative of all women with menopause

APPENDIX 4: Summary of Findings

First Author, Publication Year	Main Study Findings	Author's Conclusions
Perez[11] 2012 WHI (AF)	**Women who developed AF, n (annualized %)** MPA+CEE: 323 (0.70) PL: 288 (0.67) HR 1.07 (95% CI 0.91, 1.25), P=0.439 **Sensitivity analyses, HR (95% CI)** Stricter definition of AF (1 inpatient diagnosis or 2 outpatient claims): 1.01 (0.85, 1.21) Any AF: 1.07 (0.91, 1.25) AF or atrial flutter: 1.03 (0.89, 1.21) CMS enrollment at baseline: 1.10 (0.92, 1.32) WHI data alone: 1.04 (0.83, 1.30)	"We report a modest, but statistically significant increase in the risk of developing AF in women assigned to active postmenopausal hormone therapy, driven primarily by effects of CEE in women with prior hysterectomy…The absence of an increased risk of AF in women randomized to E+P [MPA+CEE] may be attributable to differences in the E+P (women with a uterus) and E-alone (women with prior hysterectomy) trial cohorts." (p. 1113, 1114)
Chlebowski[12] 2010 WHI (breast cancer)	**Invasive breast cancer incidence, n (annualized %)** MPA+CEE: 385 (0.42) PL: 293 (0.34) HR 1.25 (95% CI 1.07, 1.46), P=0.004 **Breast cancer with positive lymph nodes, n (%)** MPA+CEE: 81 (23.7) PL: 43 (16.2) HR 1.78 (95% CI 1.23, 2.58), P=0.03 **Subgroup analyses, HR (95% CI)** No prior use of combined therapy: 1.16 (0.98, 1.37) Prior use of combined therapy: 1.85 (1.25, 2.80) Interaction: P=0.03 **Death by breast cancer, n (annualized %)** MPA+CEE: 25 (0.03) PL: 12 (0.01) HR 1.96 (95% CI 1.00, 4.04), P=0.049 Censoring for women not reconsenting: HR 1.96 (95% CI 1.01, 4.05), P=0.048 Censoring at nonadherence: HR 2.96 (95% CI 1.00, 8.77), P=0.053 All-cause mortality after diagnosis: HR 1.57 (95% CI 1.01, 2.48), P=0.45 Inverse probability weighting: HR 2.22 (95% CI 1.07, 4.59)	"In the WHI randomized, placebo-controlled trial, conjugated equine estrogen plus medroxyprogesterone acetate increased invasive breast cancer incidence, and the cancers were more commonly node-positive. There were more deaths attributed to breast cancer (2.6 vs 1.3 per 10 000 women per year) and more deaths due to all causes following a diagnosis of breast cancer (5.3 vs 3.4 per 10 000 women per year) in the combined hormone therapy group vs the placebo group." (p. 1688)
Chlebowski[13] 2009 WHI (lung cancer)	**Lung cancer incidence, n (annualized %)** MPA+CEE: 109 (0.16) PL: 85 (0.13) HR 1.23 (95% CI 0.92, 1.63), P=0.16	"In secondary analysis of a randomized, placebo-controlled clinical trial, use of CEE plus MPA did not increase lung cancer incidence but significantly increased deaths from lung cancer, the most common cause

First Author, Publication Year	Main Study Findings	Author's Conclusions
	Non-small cell lung cancer incidence, n (annualized %) MPA+CEE: 96 (0.14) PL: 72 (0.11) HR 1.28 (95% CI 0.94, 1.73), P=0.12 **Small cell lung cancer incidence, n (annualized %)** MPA+CEE: 13 (0.02) PL: 13 (0.02) HR 0.96 (0.44, 2.07), P=0.91 **Death from lung cancer, n (annualized %)** MPA+CEE: 73 (0.11) PL: 40 (0.06) HR 1.71 (95% CI 1.16, 2.52), P=0.01 **Death from non-small cell lung cancer, n (annualized %)** MPA+CEE: 62 (0.09) PL: 31 (0.05) HR 1.87 (95% CI 1.22, 2.88), P=0.004 **Death from small cell lung cancer, n (annualized %)** MPA+CEE: 11 (0.02) PL: 9 (0.01) HR 1.16 (95% CI 0.48, 2.79), P=0.75 **Death after lung cancer diagnosis, n (annualized %)** MPA+CEE: 78 (0.12) PL: 49 (0.08) HR 1.50 (1.05, 2.14), P=0.03 **Subgroup analyses by smoking status** Never: HR 2.11 (95% CI 0.64, 6.84) Current: HR 1.46 (95% CI 0.83, 2.57) Past: HR 1.81 (95% CI 0.99, 3.30)	of cancer death in women. The evidence was most consistent with combined hormone therapy influencing primarily non-small cell lung cancer with the absolute increase in risk of death from this disease of special relevance to women already at elevated risk due to smoking." (p. 5)
Sweetland[14] 2012 Million Women Study (venous thromboembolism)	**Risk of VTE compared with never users, RR (95% CI)** Oral estrogen only: 1.42 (1.22, 1.66) Oral estrogen-progestin: 2.07 (1.86, 2.32) Oral estrogen-MPA: 2.67 (2.25, 3.17) Oral estrogen-norethisterone: 1.82 (1.52, 2.17) Oral estrogen-norgestrel: 1.98 (1.71, 2.29)	"Among users of oral estrogen-progestin HT, use of preparations containing medroxyprogesterone acetate was associated with a significantly higher risk of VTE than preparations containing norethisterone/norgestrel…the main new finding here is the variation in risk of VTE between types of progestin amongst estrogen-progestin HT users, almost all of whom have not had a hysterectomy." (p. 2282, 2283)
Hitchcock[15] 2012 (vasomotor symptoms)	Adherence was determined by pill counts and diary records – 83% of women took ≥ 80% of pills for ≥ 60 d. 54% of women randomized to progesterone and 69% of women randomized to placebo correctly identified their therapy assignment.	"Oral micronized progesterone is an effective option for treating hot flushes and night sweats in healthy postmenopausal women, with decreases greater than placebo in VMS score, frequency, and severity. The difference between progesterone and placebo was clinically important and, despite a lower sample size,

First Author, Publication Year	Main Study Findings	Author's Conclusions
	Run-in VMS score, mean (95% CI) Progesterone: 18.3 (15.8, 20.8) Placebo: 15.1 (12.1, 18.0) Difference: 3.2 (-0.6, 7.1) **Final change in VMS score from run-in, mean (95% CI)** Progesterone: -10.0 (-12.0, -8.1) Placebo: -4.4 (-6.6, -2.2) Difference: -4.3 (-6.6, -1.9) **Run-in VMS frequency, mean (95% CI)** Progesterone: 7.1 (6.4, 7.9) Placebo: 6.3 (5.3, 7.3) Difference: 0.8 (-0.4, 2.0) **Final change in VMS frequency from run-in, mean (95% CI)** Progesterone: -3.3 (-3.9, -2.7) Placebo: -1.4 (-2.1, -0.8) Difference: -1.6 (-2.4, -0.8) **Run-in VMS severity (1-4), mean (95% CI)** Progesterone: 2.6 (2.5, 2.8) Placebo: 2.4 (2.2, 2.6) Difference: 0.2 (0.0, 0.5) **Final change in VMS severity from run-in, mean (95% CI)** Progesterone: -0.6 (-0.8, -0.5) Placebo: -0.4 (-0.5, -0.2) Difference: -0.2 (-0.4, 0.0) **Post-hoc subgroup analysis in women with moderate-to- severe VMS during run-in, mean difference (95% CI)** VMS score: -4.8 (-9.3, -0.4) VMS frequency: -2.0 (-3.5, -0.4) VMS severity: 0.0 (-0.5, 0.4)	was also confirmed in a subgroup analysis of women with frequent and moderate to severe VMS at baseline. There were no serious adverse events, and those experienced were as common with placebo as with progesterone." (p. 6)
Lantto[16] 2012 (heart rate variability)	In women with hot flashes, there was a higher number of supraventricular ectopic beats in the OE+MPA group compared with the OE group OE+MPA (n=17): 71 ± 128 OE (n=17): 12 ± 11 P=0.018 Comparisons between women without hot flashes were not feasible due to the low numbers with supraventricular ectopic beats in this group.	"Our findings suggest that the addition of MPA to oral E2 in women with hot flashes may lead to an increased occurrence of supraventricular ectopic beats…Excessive supraventricular ectopic activity is associated with an increased risk of atrial fibrillation and stroke." (p. 87)

AF = atrial fibrillation; CEE = conjugated equine estrogens; CI = confidence interval; CMS = Centers for Medicare & Medicaid Services; HR = hazard ratio; MPA = medroxyprogesterone acetate; PL = placebo; RR = relative risk; WHI = Women's Health Initiative