# Complete Summary

## GUIDELINE TITLE

Role of progestogen in hormone therapy for postmenopausal women: position statement of The North American Menopause Society.

## BIBLIOGRAPHIC SOURCE(S)

Role of progestogen in hormone therapy for postmenopausal women: position statement of The North American Menopause Society. Menopause 2003 Mar-Apr;10(2):113-32. [173 references] PubMed

## GUIDELINE STATUS

This is the current release of the guideline.

## COMPLETE SUMMARY CONTENT

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## SCOPE

### DISEASE/CONDITION(S)

Postmenopause

### GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Management
Prevention
Risk Assessment
Treatment

### CLINICAL SPECIALTY

Endocrinology
Family Practice
Geriatrics
Internal Medicine
Obstetrics and Gynecology
Preventive Medicine

## INTENDED USERS

Advanced Practice Nurses
Allied Health Personnel
Health Care Providers
Health Plans
Managed Care Organizations
Physician Assistants
Physicians

## GUIDELINE OBJECTIVE(S)

- To create an evidence-based position statement regarding the role of progestogen in postmenopausal hormone therapy (estrogen plus a progestogen, or EPT) for the management of menopause-related symptoms
- To provide an update on clinical information relating to progestogens and offer a reasonable approach regarding their use in combination with estrogen in postmenopausal women

## TARGET POPULATION

Postmenopausal women in North America

## INTERVENTIONS AND PRACTICES CONSIDERED

1. **Determination of candidacy for treatment**
2. **Selection of treatment product, such as**:

   *Progestogens*:

   - Progesterone (micronized)
     - Oral capsule (Prometrium)
     - Vaginal gel (Prochieve)
   - Progestin

     Oral tablet

     - medroxyprogesterone acetate (Provera, Gen-Medroxy, Alti-MPA, Novo-Medrone)
     - norethindrone or norethisterone (Micronor, Nor-QD)
     - norethindrone acetate (Aygestin, Norlutate)
     - norgestrel (Ovrette)

     Intrauterine system

- levonorgestrel

*Combination estrogen-progestin products*

- Oral continuous-cyclic regimen
  - Conjugated equine estrogens PLUS medroxyprogesterone acetate (Premphase)
- Oral continuous-combined regimen
  - Conjugated equine estrogens PLUS medroxyprogesterone acetate (Prempro, Premplus)
  - Ethinyl estradiol PLUS norethindrone acetate (Femhrt)
  - 17beta-estradiol PLUS norethindrone acetate (Activella)
- Oral intermittent-combined regimen
  - 17beta-estradiol PLUS norgestimate (Ortho-Prefest)
- Transdermal continuous-combined regimen
  - 17beta-estradiol PLUS norethindrone acetate (CombiPatch, Estalis)
- Transdermal continuous-cycle regimen
  - 17beta-estradiol PLUS norethindrone acetate (Estalis Sequi, Estracomb)

3. **Management of side effects by tailoring progestogen type, dosage, or rate of administration, or the EPT regimen**.

### MAJOR OUTCOMES CONSIDERED

Benefits and risks of adding progestogens to estrogen therapy in postmenopausal women, the clinical goal of which is to provide endometrial protection while maintaining estrogen benefits and minimizing progestogen-induced sided effects, particularly uterine bleeding.

## METHODOLOGY

### METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

### DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

For this position statement, a search was performed of the medical literature on progestogen use in postmenopausal women using the database MEDLINE. Priority was given to evidence from randomized, controlled clinical trials and meta-analyses of such trials followed by evidence from controlled observational studies, using criteria described elsewhere. Conclusions from other evidence-based guidelines also were reviewed.

### NUMBER OF SOURCE DOCUMENTS

Not stated

### METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)

## RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not stated

## METHODS USED TO ANALYZE THE EVIDENCE

Review
Review of Published Meta-Analyses

## DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

An editorial board composed of experts from both clinical practice and research was enlisted to review the published data and compile supporting statements and conclusions. If the evidence was contradictory or inadequate to form a conclusion, a consensus-based opinion was made.

## METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

## DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Clinicians and researchers acknowledged to be experts in the field of postmenopausal hormone therapy were enlisted to review the evidence obtained from the medical literature and develop a position statement for approval by The North American Menopause Society (NAMS) Board of Trustees. If the evidence was contradictory or inadequate to form a conclusion, a consensus-based opinion was made.

## RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

## COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

## METHOD OF GUIDELINE VALIDATION

Internal Peer Review

## DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

The Board of Trustees of The North American Menopause Society (NAMS) reviewed this manuscript and approved it in November 2002.

## RECOMMENDATIONS

### MAJOR RECOMMENDATIONS

Progestogen should be added to estrogen therapy (ET) in all postmenopausal women with an intact uterus to prevent the elevated risk of estrogen-induced endometrial hyperplasia and adenocarcinoma. All U.S. Food and Drug Administration (FDA)-approved progestogen formulations will provide endometrial protection if the dose and duration are adequate. Evidence is lacking to recommend topical progesterone preparations for preventing estrogen-induced endometrial hyperplasia.

#### EPT Regimens

The clinical goal of estrogen plus progestogen therapy (EPT) regimens is to provide uterine protection, maintain estrogen benefits, and minimize side effects (particularly uterine bleeding, which is annoying to many women and often reduces compliance), although there is no consensus on how to accomplish this goal. Regimens may be classified into the following types: cyclic, cyclic-combined, continuous-cyclic, continuous long-cycle, continuous-combined, and intermittent-combined (refer to Table 4 in the original guideline document for details on the definitions of EPT regimens).

Standard EPT regimens provide adequate endometrial protection. There is less long-term experience with intermittent-combined and continuous long-cycle regimens, and more study is required to fully ascertain efficacy and safety. Some cyclic regimens may be less effective than continuous regimens in inhibiting the development of uterine cancer. With cyclic and continuous-cyclic regimens, withdrawal uterine bleeding occurs in about 80% of women when progestogen is stopped, although many women on continuous-cyclic regimens become amenorrheic within 12 months. Continuous-combined regimens avoid withdrawal bleeding, but breakthrough uterine bleeding occurs in nearly 40% of women during the first 6 months. Nearly 90% of women on this regimen become amenorrheic within 12 months. Persistent breakthrough bleeding with continuous-combined EPT may necessitate switching to another regimen. Pulsed regimens have 1-year amenorrhea rates of nearly 80%. Some women using a cyclic ET regimen experience hot flashes during the estrogen-free period; regimens with continuous estrogen administration usually avoid hot flashes.

#### Effects on other Organ Systems

##### Cardiovascular System

Because of clinical trials (primarily the Women´s Health Initiative [WHI] and the Heart and Estrogen/Progestin Replacement Study [HERS]) reporting significantly increased risks with EPT, The North American Menopause Society (NAMS) recommends not initiating any ET or EPT regimen for the primary or secondary prevention of coronary heart disease (CHD), although the effect of ET on CHD is not yet clear. However, observational studies have shown that ET has beneficial effects on atherosclerosis, vasodilation, plasma lipids, arterial response to injury, and insulin sensitivity. Although adding some progestogens may diminish these

beneficial effects, in general, they do not eliminate them. Selecting a metabolically neutral progestogen for EPT, such as micronized progesterone or norgestimate, is recommended to maintain higher plasma high-density lipoprotein cholesterol (HDL-C). In animal studies, progestins with a higher androgenic potency reduce more of the beneficial effects of estrogens on vasodilation; progesterone and 19-norpregnane derivatives have less of an adverse effect. For women with diabetes mellitus (DM) who are using EPT to treat acute menopausal symptoms, continuous-cyclic EPT regimens are recommended to minimize progestogen exposure; low-dose oral micronized progesterone is also recommended.

**Skeleton**

Although adding 2.5 mg medroxyprogesterone acetate (MPA) or 1 mg norethindrone acetate (NETA) to ET slightly enhances estrogen´s ability to prevent bone mineral density (BMD) loss in early postmenopausal women, estrogen alone is adequate to maintain BMD. EPT reduces spine and hip fractures, but the role of progestogen in this effect is not known. The decision to add progestogen to ET should not be based on its skeletal impact.

**Breast**

Breast cancer risk is not decreased when progestogen is added to hormone therapy, and emerging data suggest that there may be an increased risk with standard doses. However, the overall risk (approximately 30% increase) does not seem to affect mortality. Mammographic density is increased with progestogen use, although this effect will reverse with discontinuation of use. Breast discomfort and pain may increase with progestogen use.

**Central Nervous System**

Negative effects on mood can occur when progestogen is added to hormone therapy. Data are inadequate to recommend specific progestogens or EPT regimens for minimal adverse effects.

Therapeutic Management

The clinical goal of progestogen therapy when added to ET is to provide endometrial protection while minimizing unwanted side effects. As with any pharmaceutical agent, therapy should be tailored to a woman´s individual needs. The only menopause-related indication for chronic progestogen use seems to be endometrial protection from unopposed estrogen therapy. NAMS recommends that clinicians prescribe adequate progestogen for all postmenopausal women with an intact uterus who are using ET; postmenopausal women without a uterus should not be prescribed a progestogen.

Studies have better defined the necessary dose and duration of the progestogen course to oppose the estrogen-induced risk of endometrial hyperplasia and adenocarcinoma. All of the FDA-approved progestogen formulations will provide endometrial protection if the dose and duration are adequate (refer to Table 5 of the original guideline document for the minimum progestogen dosing

requirements for endometrial protection with standard estrogen dosing). Larger or smaller estrogen doses may require larger or smaller progestogen doses, respectively. However, the risk for endometrial cancer is never eliminated in women with a uterus, as women not using hormones can develop this disease. Long-term surveillance is necessary, even in women receiving appropriate doses of progestogen. Because of concern that adding progestogen may increase breast cancer risk and may attenuate some benefits of ET, the lowest appropriate dose of progestogen should be used. Use of EPT should be limited to the shortest duration consistent with treatment goals, benefits, and risks for the individual woman.

**Side Effects**

While using EPT, some women may experience uterine bleeding for months or years. Bleeding may be partially due to anatomic conditions (e.g., polyps, fibroids). If bleeding on continuous-combined or pulsed EPT persists beyond 6 months, endometrial cancer must be ruled out through tissue evaluation and/or hysteroscopy. Endometrial thickness measured by ultrasonography does not always correlate with histology of the endometrium obtained from a biopsy, although an endometrial thickness of less than 4 mm on vaginal ultrasound can be reassuring if endometrial biopsy cannot be performed.

In general, the side effects of adding progestogen to estrogen therapy are mild, although they may be severe in a small percentage of women. By tailoring progestogen type, dosage, or rate of administration, or the EPT regimen, most women who require therapy can obtain benefits with minimal side effects.

Hormone-related headaches may be lessened or eliminated by reducing estrogen fluctuation (e.g., switching from a cyclic to a continuous-combined regimen or switching from an oral to a transdermal product). In women whose headaches are exacerbated by progestogen, a better choice may be progesterone or a 19-norpregnane.

Low doses of transdermal, vaginal, or intrauterine progestogen formulations may have metabolic advantages over higher doses or oral progestogens, especially progestins derived from 19-nortestosterone. If oral therapy is preferred, the 19-norpregnanes seem to be free from metabolic side effects.

During initial progestogen therapy (particularly with oral micronized progesterone), bedtime dosing is advised to avoid the dizziness and/or drowsiness that some women experience.

**Summary**

The primary role of progestogen in hormone therapy is to protect the endometrium from hyperplasia and adenocarcinoma associated with unopposed estrogen therapy (ET). Adding the appropriate dose and duration of progestogen (either as progestin or progesterone) to ET has been shown to lower that risk to the level found in never-users of ET. The clinical goal of progestogen in hormone therapy is to provide endometrial protection while maintaining estrogen benefits and minimizing progestogen-induced side effects, particularly uterine bleeding. All FDA-approved progestogen formulations will provide endometrial protection if the

dose and duration are adequate. There are not enough data to recommend topical progesterone for this use.

A wide variety of progestogen types, routes of administration, and dosage regimens are available, each having distinct side effects, as well as different actions on the endometrium and other organ systems. Some progestogens may diminish the beneficial effects of ET on coronary heart disease and may negatively affect mood. Data on the association between progestogen use and an increased risk of breast cancer are inconsistent and controversial, but it is clear that adding progestogen to ET does not decrease breast cancer risk. Progestogen has limited effect on the bone-enhancing action of ET.

Uterine bleeding is the primary adverse effect associated with EPT. Higher rates of EPT discontinuance correlate with more uterine bleeding, and women with more days of amenorrhea have higher rates of continuance. In general, the other side effects of added progestogen are mild, although they may be severe in a small percentage of women.

There is no consensus on the preferred regimen; however, by changing the progestogen type, route, or regimen, clinicians can help minimize any attenuation of estrogen´s benefits, decrease side effects, and lessen uterine bleeding while providing adequate endometrial protection.

### CLINICAL ALGORITHM(S)

None provided

## EVIDENCE SUPPORTING THE RECOMMENDATIONS

### TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The position statement was supported by evidence from randomized, controlled clinical trials and meta-analysis of such trials, controlled observational studies, conclusions from other evidence-based guidelines. If the evidence was contradictory or inadequate to form a conclusion, a consensus-based opinion was made.

## BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

### POTENTIAL BENEFITS

The primary role of progestogen in hormone therapy is to protect the endometrium from hyperplasia and adenocarcinoma associated with unopposed estrogen therapy (ET). Adding the appropriate dose and duration of progestogen (either as progestin or progesterone) to ET has been shown to lower that risk to the level found in never-users of ET.

### POTENTIAL HARMS

Mammographic density is increased with progestogen use, although this effect will reverse with discontinuation of use. Breast discomfort and pain may increase with progestogen use.

Little is known about side effects for specific progestogens used in estrogen plus progestogen therapy (EPT). One crossover trial has shown that adverse reactions are not more frequent when medroxyprogesterone acetate (MPA) is added to estrogen therapy (ET). Mastalgia and edema may be more common with progestogens that have glucocorticoid-like activity, such as MPA and gestodene. Acne, hirsutism, and alopecia are androgen-related side effects occurring mostly with 19-nortestosterone derivatives (e.g., norethindrone [NET], levonorgestrel [LNG]). Mood swings, dizziness, and fatigue may be encountered with very high doses of oral progesterone, but at the lower doses typically used in EPT (100-300 mg), these effects are not significantly different from placebo.

Uterine bleeding is the primary adverse effect associated with EPT. Higher rates of EPT discontinuance correlate with more uterine bleeding, and women with more days of amenorrhea have higher rates of continuance. In general, the other side effects of added progestogen are mild, although they may be severe in a small percentage of women.

## CONTRAINDICATIONS

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Contraindications for progestogen therapy in a postmenopausal woman, as stated in FDA prescribing information, include thromboembolic disorders, impaired liver function, breast or genital carcinoma, undiagnosed uterine bleeding, and hypersensitivity to the drug. Some of these contraindications stem from oral contraceptive studies. There is no evidence that progestogen alone increases the risk of thrombosis. The micronized progesterone capsule (Prometrium) is contraindicated for women who are allergic to peanuts because the active ingredient is suspended in peanut oil. As with all therapies, the contraindications may not be absolute, provided that the potential benefits outweigh the potential risks, and an informed decision is made regarding acceptance of therapy.

Precautions in product labeling include careful observation of women who have a history of depression or diabetes, or when preexisting disease may be influenced by fluid retention (e.g., epilepsy, migraine, asthma, cardiac or renal dysfunction). Fluid retention has not been observed with progesterone and 19-norpregnane derivatives.

## QUALIFYING STATEMENTS

### QUALIFYING STATEMENTS

This review will not address the use of progestogens in contraceptives or the use of progestogens in pre- or perimenopausal women. Although the information regarding progestogen use is relevant internationally, the focus is limited to products available in North America.

## IMPLEMENTATION OF THE GUIDELINE

### DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

## INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

### IOM CARE NEED

Staying Healthy

### IOM DOMAIN

Effectiveness
Safety

## IDENTIFYING INFORMATION AND AVAILABILITY

### BIBLIOGRAPHIC SOURCE(S)

Role of progestogen in hormone therapy for postmenopausal women: position statement of The North American Menopause Society. Menopause 2003 Mar-Apr;10(2):113-32. [173 references] PubMed

### ADAPTATION

Not applicable: The guideline was not adapted from another source.

### DATE RELEASED

2003 Mar-Apr

### GUIDELINE DEVELOPER(S)

The North American Menopause Society - Private Nonprofit Organization

### SOURCE(S) OF FUNDING

The development of this Position Statement was supported by an unrestricted educational grant from Ortho-McNeil Pharmaceutical, Inc.

### GUIDELINE COMMITTEE

Expert Consensus Committee

### COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Editorial Board composed of Rogerio A. Lobo, MD (Chair); David F. Archer, MD; Bruce Ettinger, MD; R. Don Gambrell, Jr., MD; James H. Liu, MD; Regine Sitruk-Ware, MD; Frank Z. Stanczyk, PhD; and Janice D. Wagner, DVM, PhD

## FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

## GUIDELINE STATUS

This is the current release of the guideline.

## GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from The North American Menopause Society (NAMS) Web site.

Print copies: Available from NAMS, P.O. Box 94527, Cleveland, OH 44101, USA Order forms are available at The North American Menopause Society [NAMS] Web site, www.menopause.org

## AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- Boggs PP, Utian WH. The North American Menopause Society develops consensus opinions. Menopause 1998 Summer;5(2):67-8.

Electronic copies: Available from the NAMS Web site.

Print copies: Available from NAMS, P.O. Box 94527, Cleveland, OH 44101, USA. Order forms are available in Portable Document Format (PDF) from The North American Menopause Society Web site, www.menopause.org.

## PATIENT RESOURCES

None available

## NGC STATUS

This NGC summary was completed by ECRI on June 30, 2003. The information was verified by the guideline developer on July 23, 2003.

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