# Uterine Bleeding Rates with Hormone Therapies in Menopausal Women with Vasomotor Symptoms

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## Introduction

- Women often discontinue the use of hormone therapy (HT) taken for menopausal vasomotor symptoms (VMS) because of bleeding and spotting[1]
- The REPLENISH trial (NCT01942668) evaluated a single oral capsule combining bioidentical 17β-estradiol and progesterone (E2/P4; TherapeuticsMD, Boca Raton, FL) in postmenopausal women with a uterus seeking relief of moderate to severe VMS[2]
  - The 1 mg E2/100 mg P4 dose was FDA approved as Bijuva®[3]

## Objective

To report the incidence of amenorrhea over 1 year with this E2/P4 and other continuous-combined HT commercially available in the US for the treatment of VMS in postmenopausal women with a uterus

## Methods

- A list of FDA-approved, continuous-combined HT products indicated for menopausal women with a uterus and vasomotor symptoms was compiled
- PubMed was searched for English-language studies using the following keywords: menopause, bleeding and hormones found in the FDA-approved products
  - Estrogens: conjugated estrogens (CE) or estradiol or ethinyl estradiol
  - Progestogens: medroxyprogesterone (MPA), norethindrone acetate or norethisterone acetate (NETA), drospirenone, levonorgestrel (LNG)
- Prescribing information (PI) for these FDA-approved HT products was also obtained
- One-year bleeding data (12-13 cycles) from randomized, controlled trials and PI of the continuous-combined oral or transdermal HT with at least 25 women per treatment group were compared with those of E2/P4 in REPLENISH
  - Amenorrhea was defined as no bleeding or spotting
  - Spotting was defined as not requiring sanitary protection, while bleeding required sanitary protection

## Results

### Cumulative Amenorrhea Rates with E2/P4

- In the REPLENISH trial, rates of cumulative amenorrhea from cycles 1 to 13 increased over time with the E2/P4 1 mg/100 mg versus placebo (**Figure 1**)[2]

### Other FDA-approved, Continuous-combined HT Products

- **Table 1** lists the prescription hormone preparations included in the review based on PIs

### Overall Results from Clinical Trials and PI Data

- Proportions of women with cumulative amenorrhea over one year, amenorrhea at cycle 12-13, and mean bleeding/spotting days based on data from the clinical trials and PIs are shown in **Table 2**

**Figure 1.** Cumulative amenorrhea rates from cycle 1 to 13 with E2/P4 1 mg/100 mg vs placebo

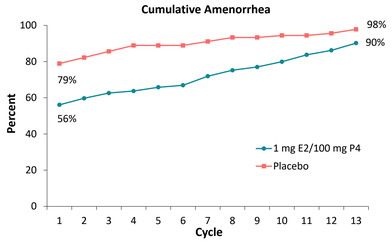



**Table 1.** FDA-approved, continuous-combined HT formulations used to treat vasomotor symptoms, included in this comparison review

| Name | Drug | Dose (mg/mg)* | Administration |
|---|---|---|---|
| Bijuva® | E2/P4 | 1/100 | Oral |
| Activella® | E2/NETA | 1/0.5, 0.5/0.1 | Oral |
| Angeliq® | E2/DRSP | 1/0.5, 0.5/0.25 | Oral |
| Prempro® | CE/MPA | 0.625/5, 0.625/2.5, 0.45/1.5, 0.3/1.5 | Oral |
| Femhrt® | EE/NETA | 5 mcg/1, 2.5 mcg/0.5 | Oral |
| Climara Pro® | E2/LNG | 0.045/0.015 | Patch |
| CombiPatch® | E2/NETA | 0.05/0.25, 0.05/0.14 | Patch |

*Except as noted. CE, conjugated estrogens; DRSP, drospirenone; EE, ethinyl estradiol; E2, 17β-estradiol; LNG, levonorgestrel; MPA, medroxyprogesterone acetate; NETA, norethindrone acetate or norethisterone acetate; P4, progesterone.

### Cumulative Amenorrhea Rates Over One Year

- E2/P4 had one of the highest cumulative amenorrhea rates over one year (56%) among the oral HT, similar to that reported for EE/NETA (2.5 mcg/0.5 mg) and E2/NETA (1 mg/0.5 mg)
- Lower cumulative amenorrhea rates were observed with transdermal HT, followed by E2/DRSP and CE/MPA (higher doses)

### Amenorrhea Rates at Cycle 12-13

- The amenorrhea rate at cycle 13 was high with E2/P4 (90%), similar to oral E2/NETA and CE/MPA (**Figure 2**)
- E2/P4 had a higher rate of amenorrhea at cycle 13 (90%) compared with the transdermal HT products (range, 40% to 65%)

### Mean Number of Bleeding/Spotting Days

- Overall, the mean number of bleeding/spotting days decreased over time with all therapies
- Mean bleeding/spotting days per cycle observed at cycle 12-13 were the lowest with oral E2/P4, followed by oral EE/NETA 5 mcg/1 mg (**Figure 3**)
- Transdermal HT products had higher mean bleeding/spotting days than oral E2/P4

**Table 2.** Summary of amenorrhea rates and number of bleeding/spotting days with FDA-approved continuous HT

| Hormone therapy (Brand name) | Type of hormone | Dose (mg/mg)* | Cumulative amenorrhea (% women) | | Mean bleeding/ spotting days/cycle (from cycle 1 to 12-13) |
|---|---|---|---|---|---|
| | | | Over one year | Cycle 12-13 | |
| **Oral** | | | | | |
| Bijuva® | E2/P4 | 1/100[3] | 56 | 90 | 1.2 to 0.7 |
| Angeliq® | E2/DRSP | 1/0.5[4,5] | 45 | 74, 83 (bleeding only) | |
| | | 0.5/0.25[6] | | 85 | 6 to 4 |
| Activella® | E2/NETA | 0.5/0.1† | NA | NA | NA |
| | | 1/0.5[6-9] | 49–59 | 75–97 | 7 to 1.8 |
| Prempro® | CE/MPA | 0.625/5[10-15] | 22–26 | 86–90 | 8 to 5.5 |
| | | 0.625/2.5[11,12,14-18] | 17–24 | 62–79 | 10 to 2 |
| | | 0.45/1.5[11,15,19] | 30–49 | 63–97 | |
| | | 0.3/1.5[11,15] | 33–45 | 68–86 | |
| Femhrt® | EE/NETA | 5 mcg/1[16,17,20, 26] | 31–36 | 87–90 | 3 to 1 |
| | | 2.5 mcg/0.5[20, 26] | 61 | 80-84 | |
| **Transdermal** | | | | | |
| Climara Pro® | E2/LNG | 0.045/0.015[21,22] | 16 | 40–41 | 4.8 to 3.6 |
| CombiPatch® | E2/NETA | 0.05/0.25[23-25] | 9–28 | 54 | 6† |
| | | 0.05/0.14[23,25] | 27 | 65 | 4† |

CE, conjugated equine estrogens; DRSP, drospirenone; EE, ethinyl estradiol; E2, 17β-estradiol; LNG, levonorgestrel; MPA, medroxyprogesterone acetate; NETA, norethindrone acetate or norethisterone acetate.
*Except as noted; †Only 6-cycle bleeding data available; ‡Mean duration of bleeding over one year.

**Figure 3.** Mean bleeding/spotting days at cycle 12-13, ranked from least to most

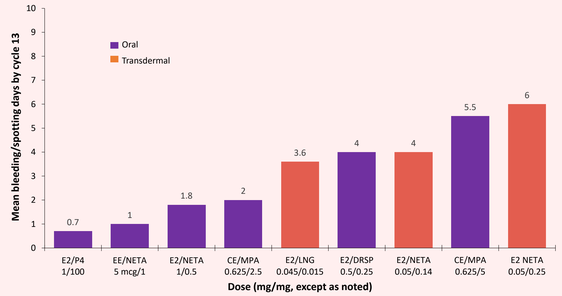
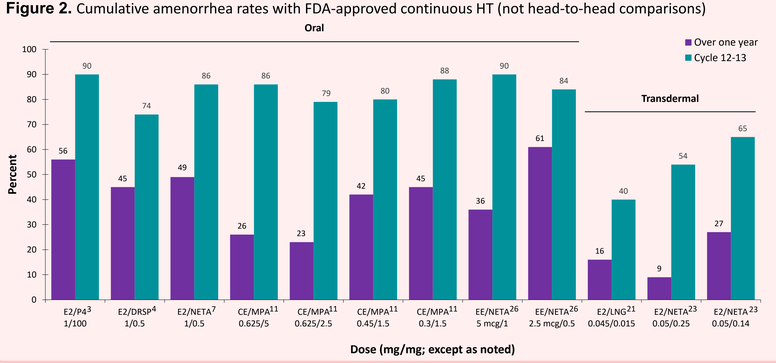



**Figure 2.** Cumulative amenorrhea rates with FDA-approved continuous HT (not head-to-head comparisons)




## Conclusions

- Compared with published bleeding data reported separately for other continuous-combined HT, E2/P4 appears to have a positive bleeding profile
  - Note that comparisons were derived from separate studies with each product and not head-to-head trials
- The high rates of cumulative amenorrhea with Bijuva make it a therapeutic option for postmenopausal women seeking treatment for moderate to severe VMS who are concerned about bleeding

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## Disclosures

- JHP consults for Pfizer, Shionogi, and TherapeuticsMD; and has stock options with TherapeuticsMD. DFA consults for AbbVie, Actavis, Agile Therapeutics, Bayer Healthcare, Endoceutics, Exeltis, InnovaGyn, Merck, Pfizer, Radius Health, Sermonix, Shionogi, Teva Women's Healthcare, and TherapeuticsMD; and has received research support from Actavis, Bayer Healthcare, Endoceutics, Glenmark, Merck, Radius Health, Shionogi, and TherapeuticsMD. SRG is on the advisory board of AbbVie, AMAG, and TherapeuticsMD; consults for Cook ObGyn, Cooper Surgical, and IBSA; and is on the speaker's bureau for AMAG, Duchesnay, and TherapeuticsMD. RK consults for Allergan, Cooper Surgical, Duchesnay, Lupin, Noven, Procter & Gamble, Radius Health, and TherapeuticsMD and is on the speaker's bureau of AMAG, Cooper Surgical, and TherapeuticsMD. BB, and SM are employees of TherapeuticsMD with stock/stock options. BB is also a Board member of TherapeuticsMD.
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