



Individual Approach to Hormone Replacement Therapy – A Computer Assisted Method of Assessment of the Minimal Useful Dose

BM Petrikovsky*

Professor and former Chair of Obstetrics and Gynecology, Nassau University Medical Center, USA

***Corresponding author:** BM Petrikovsky, Professor and former Chair of Obstetrics and Gynecology, Nassau University Medical Center, USA.

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Short Communication

Estrogen replacement therapy (ERT) was primarily used to treat vasomotor symptoms, it had been increasingly viewed as a way to prevent chronic diseases of aging, including coronary heart disease (CHD), cognitive impairment and osteoporosis [1-3]. Osteoporosis leads to bone fractures. Death rate due to osteoporosis is higher than the mortality rate attributed to breast and endometrial cancer combined. Estrogens are considered the gold standard in assessing the efficacy of various medications in osteoporosis treatment [1,2]. At least 40% of postmenopausal women in the United States were using ERT before the publication of the Women's Health Initiative (WHI) report, which addressed the risks and benefits of ERT [1,4]. WHI trials addressed the most commonly used hormone formulations at the time in the United States -- conjugated equine estrogen (CEE) plus medroxyprogesterone acetate (MPA). Findings from these trials have been extensively published during the past decades [5-7].

Manson et al. [1] conducted an extensive study involving 27,347 postmenopausal women aged 50 to 79 years from 1993 to 1998 at 40 US medical centers; 16,608 women with uterus present were randomized to oral CEE (0.625 mg/d) plus MPA (2.5 mg/d) (Prempro) or placebo, and 10,739 women with prior hysterectomy were randomized to oral CEE (0.625 mg/d) alone (Premarin) or placebo. CHD and invasive breast cancer served as primary outcomes. The study results were summarized as follows: For every 10,000 women taking CEE plus MPA per year, there were 6 more coronary events, 9 more strokes, 9 more pulmonary emboli, 9 more cases of breast cancer compared to the placebo group, and 6 fewer cases of colorectal cancer, 1 fewer case of endometrial cancer, 6 fewer hip fractures, and 1 fewer death compared to the placebo group [1].

In menopausal women aged 50-54 years with moderate or severe hot flashes, night sweats, administration of both the CEE and MPA and CEE alone caused substantial reductions in symptoms (64% and 28%, respectively, vs placebo at 1 year). ERT was also associated with statistically significant benefits for physical functioning and general health [1]. Almost half of women aged 60 to 65 years without HRT reported menopausal complaints and nearly two thirds experienced sexual dysfunction [8,9].

Most of the researchers emphasized the importance of developing individual minimal effective dose for each patient with the goal to treat her symptoms and decrease the risk of complications. Shuffell et al. [10] studied the risk of breast cancer in HRT users and concluded that the lower breast cancer risk extends to lower doses of ERT preparation [10].

In 2008 [11] we developed a computer algorithm (copyright RS 1800) to provide individual minimal effective dose for a patient calculated based on the following major parameters: Age, weight, uterine status (present, absent), individual hormonal levels (estradiol, testosterone) symptoms – minimal, moderate, severe. Bone health: Normal bone, minimal bone loss, osteopenia, osteoporosis. Those parameters were chosen because based on data in the literature and our experience they appear to be most important for patients' wellbeing [1,3,5,11]. Patient symptoms are also taken into consideration in order of priorities. When enrolling into the program, patients are asked to list and rank their symptoms and concerns, e.g., some reported severe hot flashes but were more worried about bone health. The computer program was designed to develop the minimal effective dose of HRT to address the needs of individual patients (e.g., bone loss, hot flashes, vaginal dryness, etc.) Progestins were added if indicated. The computer algorithm is

applicable to all forms of ERT, including pills, jells, sprays, injections, creams, patches, among others. The majority of our patients were using skin patches because oral estrogens first metabolize in the liver, resulting in higher conversions of E2 to estrone. Transdermal estrogens avoid liver metabolic pathways [10]. Vaginal creams and gels also appear to be a safer form of estrogen compared to pills according to the study conducted by Shilpa et al. [11] These authors examined the association between vaginal estrogen use and multiple health outcomes (myocardial infarction, stroke, and pulmonary embolism/deep vein thrombosis), cancer (breast, endometrial, ovarian, and colorectal cancer), and hip fractures. They included postmenopausal women from the Nurses' Health Study (1982-2012). Authors concluded that vaginal estrogen use was not associated with a higher risk of cardiovascular disease or cancer and was an effective treatment for genitourinary syndrome

of menopause (GSM) [11]. GSM occurs in up to 45% of peri and postmenopausal women adversely impacting physical and sexual health. Vaginal estrogen therapy allows for the restoration of the vaginal epithelium with an increase in the number of superficial cells and normalization of acidic pH, which restores the normal flora and decreases vaginal dryness and dyspareunia [13]. The North American Menopausal Society and the American College of Obstetricians and Gynecologists (ACOG) recommend that low-dose vaginal estrogens be used to treat the symptoms [12,13].

We didn't use vaginal cream as a main form of ERT because of the difficulty to measure an appropriate amount of medication. We used a transdermal patch of estradiol in a multipolymeric adhesive (Minivelle, Noven Pharmaceutical LLC)

These patches come in 0.025, 0.0375, 0.05, 0.075, 0.1 mg dosages preparations (Figure 1).

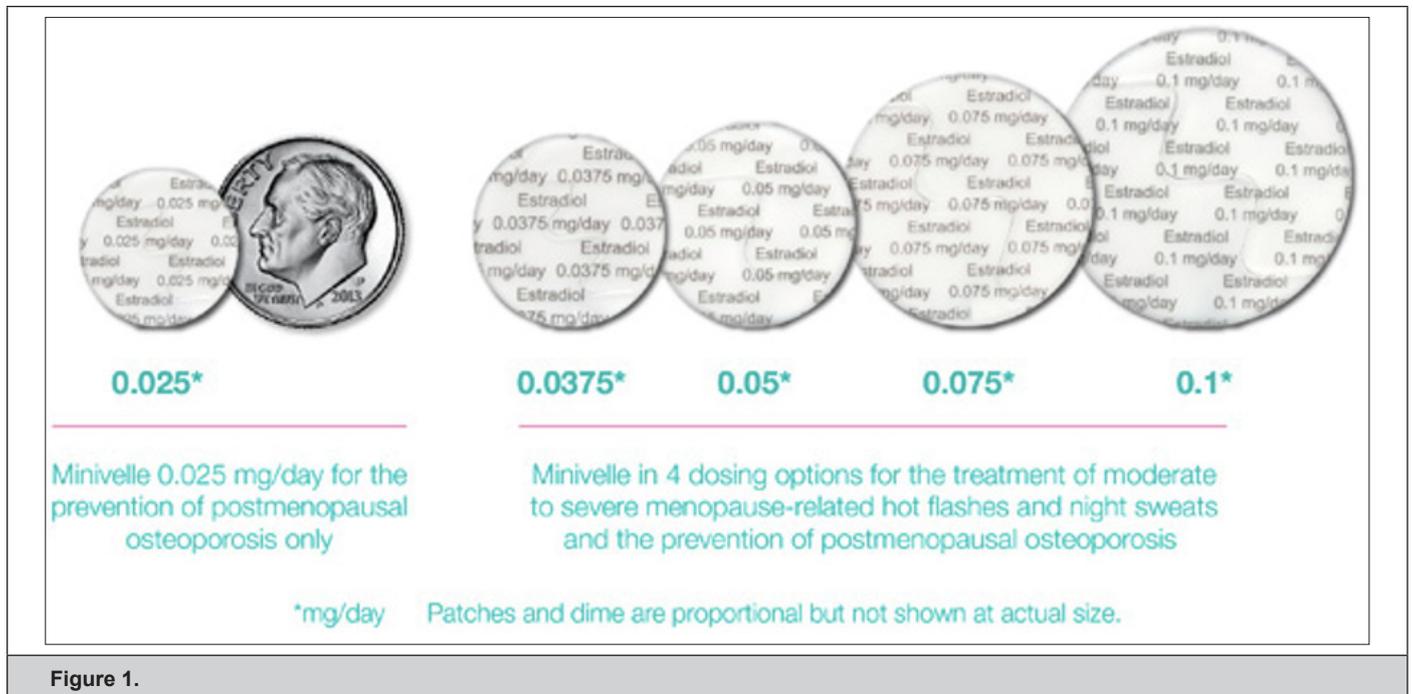


Figure 1.

Below are examples of the practical use of computer-assisted dose selection.

Patient 1:

- Age: 62
- Weight: 78 kg
- Uterus: Present
- Menopausal symptoms: Severe
- Hormonal levels:
 - FSH: 35 mIU/mL
 - Estradiol: 22 pg/mL
 - Testosterone: 18 mg/dL

f. Dose of Minivelle: 95% of the patch square surface as suggested by the computer algorithm after patient's parameters were loaded into the system.

Patient 2:

- Age: 48
- Weight: 92 kg
- Uterus and ovaries removed
- Menopausal symptoms: Minimal, desires bone protection
- Hormonal levels:
 - FSH: 22 mIU/mL
 - Estradiol: 28 pg/mL

- c. Testosterone: 33 mg/dL
- 6. Computer recommended dose is 52% of the patch square surface.

Reassessment is suggested every year since many parameters (age, weight, severity of symptoms) are subject to change.

Patient 3:

- a. Age: 56
- b. Weight: 73 kg
- c. Uterus: Removed
- d. Menopausal symptoms: severe
- e. Hormonal levels:
 1. FSH: 40 mIU/mL
 2. Estradiol: 30 pg/mL
 3. Testosterone: 15 mg/dL
- f. Dose: 87% of the patch square surface

The same patient 10 years later:

1. Age: 66
2. Weight: 82 kg
3. Menopausal symptoms: minimal to none
4. Dose: 28% of the patch square surface

In summary, we report what appears to be the first experience with utilization of a computer program for an individual approach to ERT. The program does not prescribe ERT but rather adjusts the dose to the needs of the individual patient. Because benefits and side effects are usually dose related, the goal of the program is to offer minimally effective dose. The decision of when and if a patient should be started on ERT remains solely hers and her healthcare providers.

Conclusion

We presented what appears to be the first attempt to use computer algorithm for selecting a minimum useful dose of ERT based on parameters (weight, age, symptoms, etc.) and treatment priorities of an individual patient. We hope that in the near future, patients would be able to input their personal data on a website and receive a minimal individualized effective dose. The website's recommendations will under no circumstances replace the patient's clinicians. The final decision on the type and dose of ERT will be of the patient's healthcare provider.

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