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REVIEW

Primary choice of estrogen and progestogen as components for HRT: a clinical pharmacological view

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ABSTRACT

Prescribing hormone replacement therapy (HRT) requires consideration of the selection of its two components, the estrogen and the progestogen. In terms of the estrogen, the decision is mainly whether to use estradiol (E2) or conjugated equine estrogens (CEE). These are the components needed to efficiently treat climacteric symptoms or/and prevent osteoporosis, currently the only labeled indications. There is still controversy regarding the adequate dosages comparing E2 and CEE; however, the consensus is that the differences in the efficacy of E2 and CEE are not a real issue. Therefore, other criteria have to be used. The first reason to add the progestogen is to avoid the development of endometrial cancer (i.e. to achieve 'endometrial safety'). Any available 'fixed-combined' HRT preparation has to be tested for sufficient endometrial efficacy, because the first question the health authorities ask before product registration relates to endometrial safety. We can generally rely on the endometrial safety of these fixed-combined products. However, it could be that we want to use 'free' combinations, which are necessary if we use transdermal E2 (patches, gel, spray), but also to individualize schedules, for example when treating bleeding problems. The question here is how to attain knowledge about the endometrial efficacy of the different progestogens and how to monitor therapy. We will try to answer these two questions from a 'clinical pharmacology' point of view, as a discipline which preferably considers pharmacological properties, but also relating to clinical practice, to achieve individualized therapy with optimal efficacy, best tolerability and minimal risks.

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Which studies should we use for the choice of HRT?

Often the belief is that only randomized controlled trials should be considered. However, reviews in the *NEJM* which analyzed about 150 studies [1,2] and compared observational studies and randomized controlled trials found that conclusions cannot be drawn from the best hierarchy of research designs. We only have one study for hormone replacement therapy (HRT) as the 'gold standard', the Women's Health Initiative (WHI) trial; that is, a prospective randomized placebo-controlled study, with sufficient statistical power for clinical endpoints such as cardiovascular benefit or risk of breast cancer [3,4]. However, dozens of publications have pointed out the limitations of this study.

In the WHI, only one estrogen and one progestogen were used, conjugated equine estrogens (CEE) and medroxyprogesterone acetate (MPA), both in only one dosage (CEE 0.625 mg/day; MPA 2.5 mg/day) in a continuous-combined design. Extrapolation to clinical practice is difficult, because other HRT preparations are generally used more now, with estradiol (E2) instead of CEE and about a dozen other progestogens. In our countries (China and Germany), the more 'natural' progestogens progesterone or its retro-isomer dydrogesterone are used.

Furthermore, the WHI tested HRT in the 'wrong' population, starting at the age of 63 years in two-thirds of the women. It is the general consensus that HRT should be started during the perimenopause or early postmenopause, and 40–50% of the study population were at high risk of cardiovascular disease or breast cancer, with risk factors such as obesity, smoking, hypertension, dyslipidemia and so on. Regarding studies addressing the choice of HRT, it must be added that today, like many other physicians, we use transdermal E2 to reduce risks such as venous thromboembolism, stroke or gallbladder diseases, and many prefer progesterone as the progestogen component, even if these two components of HRT have to be combined in 'free combination' [5,6]. No randomized controlled trials have been published which test this combination with sufficient statistical power for clinical endpoints. Assessments from the results of the WHI must be made with caution, as recently described within an excellent review in this journal [7]. Therefore, we should also consider observational studies and pharmacological criteria, including experimental research, to decide on the choice of the two components of HRT.

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Choice of the estrogen: use of CEE still up to date?

One of the basic principles in pharmacology is to demonstrate the dose/efficacy related to the drug in use. It is indeed impossible to verify this principle by using CEE, because CEE is a mixture, mostly listed with 10 estrogenic steroids, all with biological activity which also is elicited by most of their metabolites, and all components vary in percentual composition. Members of Wyeth-Ayerst Women's Health Research published about 'insights into the varying activity' of CEE, presenting a high-performance liquid chromatography chromatogram that identifies not only 16 estrogenic components, but also at least five progestogenic and three androgenic substances [8] (Figure 1).

Tables 1 and 2 present the chemical names of these substances [9], and Figure 2 shows the chemical structure of those 10 estrogens which are officially registered by the health authorities as components of the CEE mixture.

The actions of the components differ widely, depending on clinical endpoints such as action on the vagina or uterus (mostly used for describing estrogenic action) or the important action on the vasculature, bone or breast [10]. In terms of receptor or gene activation, nowadays often used to investigate biological potency, it is not possible to extrapolate from estrogen receptor (ER)-binding affinities to biological 'intrinsic' action, and an example is presented in Table 3 [8].

The ranking 1–10 of the 10 estrogens in the mixture does not correlate with the ranking to produce a biological effect in terms of activating the main gene to turn on the C3-promotor [8]. For example, Δ(8,9)-dehydroestrone, which ranks ninth out of 10 in terms of ER-binding affinity, ranks second after 17β-estradiol regarding its ability to activate the C3-promotor. Another example of different ranking is the activation of the estrogen response element, where estrone ranks secondly, which does not correlate with its clinically well-known relative weak typical estrogenic effects as assessed in the vagina and uterus [8].

CEEs are primarily produced by extraction from the urine of pregnant mares (which may also raise the question of animal welfare), where the lowest layer contains 50–65% sodium estrone sulfate, the middle layer contains up to 30% different (not all specified) equine (i.e. not human) estrogens and the upper layer contains the second important content of the mixture, 20–35% sodium equilin sulfate. The main components of CEE, as well as of so-called 'conjugated estrogens' (also from horses or in part synthetically produced), are sodium estrone sulfate and sodium equilin sulfate. These components can vary between 52.5–61.5% and 22.5–30.5%,

Table 1. Estrogens within the CEE mixture[a].

Estrogen	%	*Approximate % of total dose*
According to the labeling		
Estrone	45	40–60
Equilin	25	15–30
17α-Dihydroequilin	15	10–20
Δ(8,9)-estrone	3.5	
17β-Estradiol	1–2	
17α-Estradiol	1–2	
17β-Dihydroequilin	1–2	
Equilenin	1–2	
17α-Dihydroequilenin	1–2	
17β-Dihydroequilenin	1–2	
Not specified in the labeling (percentages varying and unclear)		
17α-Dihydro-Δ(8,9)-estrone	–	
17β-Dihydro-Δ(8,9)-estrone	–	
2-Hydroxyestrone	–	
2-Methoxyestrone	–	
5,7,9(10)-Estratrien-3β,17β-diol	–	
3β-Hydroxy-5,7,9(10)-estratrien-17-one	–	
3β-Hydroxy-5(10),7-estradien-17-one	–	

[a]Components of Premarin, all as sodium sulfates.
Adapted from Stanczyk [9]. CEE, conjugated equine estrogens.

Table 2. Other steroids identified in the CEE mixture[a].

Steroid	%
Progestogens (not specified in the labeling; concentrations unclear)	
5α-Pregnan-3β,20β-diol	–
5α-Pregnan-3β,20β-diol	–
3β-Hydroxy-5α-pregnan-20-one	–
5α-Pregnan-3β,20β-diol	–
3β-Hydroxy-5α-pregn-16-en-20-one	–
5α-Pregnan-3β,16α,20α-triol	–
20α-Dihydro-4-pregnen-3-one	–
Androgens (not specified in the labeling; concentrations unclear)	
3β-Hydroxy-5α-androstan-16-on	–
5α-Androstan-3β,16α-diol	–
5α-Androstan-3β,16β-diol	–
5α-Androstan-3β,17β-diol	–

*Components of Premarin, all as sodium sulfates.
Adapted from Stanczyk [9]. In total, more than 200 substances including other steroids like glucocorticoids. CEE, conjugated equine estrogens.

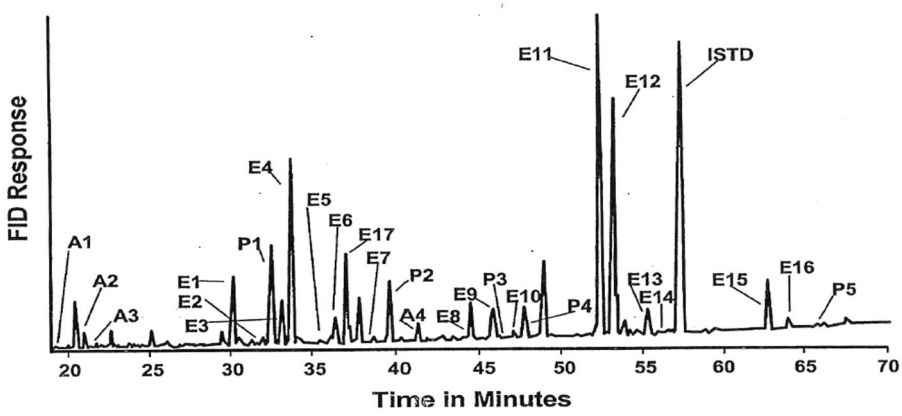

Figure 1. Chromatogram identifying the complex and varying mixture of steroids in conjugated equine estrogens (CEE). According to Dey et al. [8]. A, androgens; E, estrogens; FID, flame ionization detector; ISTD, internal standard; P, progestogens.

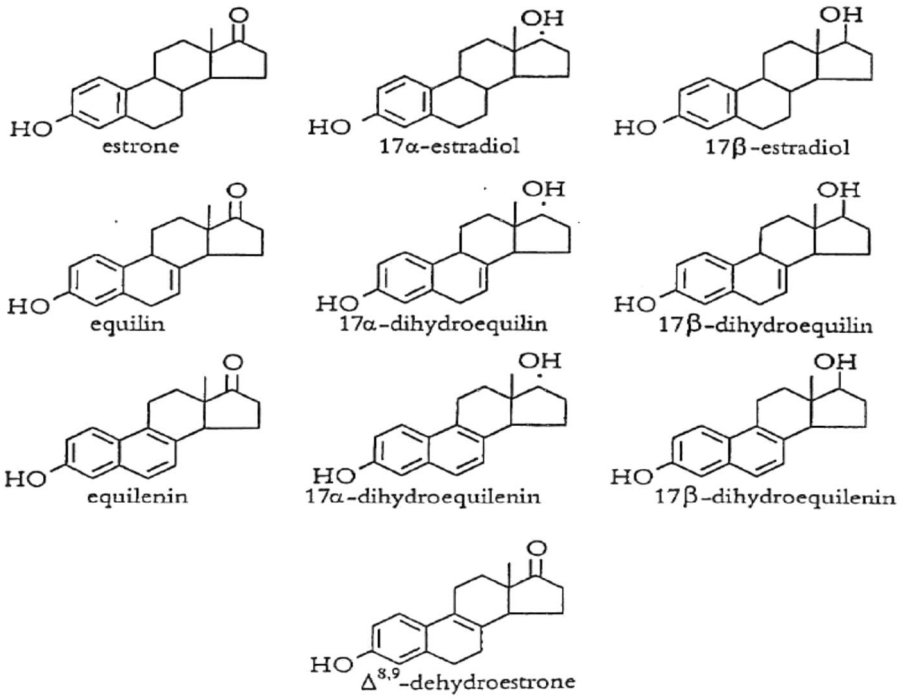

Figure 2. Chemical structure of the 10 estrogens in the conjugated equine estrogens (CEE) mixture officially registered by the health authorities. According to Lippert et al. [10].

Table 3. Relative ER-binding affinities and potency of ER and gene activation of the CEE components (components listed according to the labeling).

Rank	*Human ER-binding*	*Gene activation C3-promoter*
1	17β-Estradiol	17β-Estradiol
2	17β-Dihydroequilin	8,9-Dehydroestrone
3	17β-Dihydroequilenin	Estrone
4	17α-Dihydroequilin	17β-Dihydroequilenin
5	17α-Estradiol	Equilenin
6	Estrone	17β-Dihydroequilin
7	Equilin	Equilin
8	17α-Dihydroequilenin	17α-Dihydroequilin
9	8,9-Dehydroestrone	17α-Dihydroequilenin
10	Equilenin	17α-Estradiol

According to Dey et al. [8]. CEE, conjugated equine estrogens; ER, estrogen receptor.

Table 4. Experimental research (ovariectomized rats) on biological activity in the vagina and uterus and relative binding affinities (RBA) for ERα and Erβ related to the 10 components of CEE.

		Relative potency (%)		*RBA (%)*	
Compound	*Proportion (%)*	*Vagina*	*Uterus*	*ERα*	*ERβ*
CEE	100.0	38	100	?	?
17β-Estradiol	0.6	100	100	100	100
Estrone	49.1	30	32	26	52
Equilin	22.8	42	80	13	49
17α-Dihydroequilin	13.5	0.06	2.6	42	32
17β-Dihydroequilin	1.5	83	200	113	108
Δ(8,9)-estrone	3.9	?	?	19	32
17α-Estradiol	3.7	0.11	3.5	19	42
Equilenin	2.8	1.3	11.4	15	29
17α-Dihydroequilenin	1.6	0.018	1.3	20	49
17β-Dihydroequilenin	0.7	0.21	9.4	68	90

According to Kuhl [14,table 8; p.28]. CEE, conjugated equine estrogens; ER, estrogen receptor.

respectively, according to the United States Pharmacopeia 27 (USP 27) defined in *Martindale* [11], one of the main sources for clinical pharmacologists regarding the description of drug properties. The total of the combined two should be between 79.5 and 88% [11]. For standardization, the registration offices only ask in terms of these two estrogens. In addition, these mixtures should contain 13.5–19.5% 17-α-dihydro-equilin, 2.5–9.5% 17-α-estradiol and 0.5–4.0% of 17β-dihydro-equilin, all as sulfates [11].

Other components are not further specified by percentual content, mostly less than 1–3%, despite the fact that they may have strong biological activities. CEE have been used since the 1960s, and it took years to describe all known listed components. For example, Δ(8,9)-estrone was discovered in the mid-1970s, but was only added to the official mixture of CEE in the 1990s. Its use in the treatment of postmenopausal women showed typical estrogenic effects, even in small doses [12]. From a pharmacological point of view, we would have preferred the development of such monosubstances with the demonstration of a clear dose/efficacy/risk relationship to use as a drug rather than the present treatment with a widely unclear mixture of substances.

Remarkably, the content of 17β-estradiol is only about 1%. It is produced by the metabolism of estrone, the amount of which, however, is dependent on the activity of 17β-reductases differing in the target tissues such as the brain, bone, urogenital tract and vasculature. Likewise, other components can also function as prodrugs for active metabolites. Equilin can be metabolized to 17β-dihydroequilin (and vice versa) or to equilenin [13], both with strong biological activities, as presented in Table 4 [14]. This table summarizes several experimental studies in ovariectomized rats, showing the mean percentages of the CEE components used in these studies and the biological activity with respect to the potency in the vagina and uterus. The strong efficacy of these equine estrogens has been also shown in a variety of clinical studies with different results according to different

endpoints. For example, equilenin increased the hepatic proteins high density lipoprotein-cholesterol, SHBG, CBG and angiotensinogen to a six or seven-times higher extent than the use of 17β-estradiol [14]. These effects are not dependent on the binding affinity to these proteins, which is about 30% lower for equilenin compared to 17β-estradiol [14].

The 17-keto-components of CEE such as estrone sulfate, equilin sulfate and Δ(8,9)-estrone sulfate in general are metabolized by postmenopausal women to the more potent 17β-reduced products. Thus, a large amount of CEE components function as 'prodrugs', which highlights the problem for predicting pharmacodynamic actions, because these are strongly dependent on endogenous properties such as resorption, metabolization rates, interaction and so on [12]. Each of the components in the mixture and each metabolite has its own activity profile, and they also differ widely in their pharmacokinetic properties such as half-lives, area and curves, distribution volumes, protein binding in the blood and renal/hepatic clearance [12].

Table 4 presents the different binding activities to ERα and ERβ [14]. It was suggested that binding to ERβ could provide beneficial estrogenic effects, inducing cardiovascular prevention mechanisms or decreasing proliferation effects in the breast with the consequence of reducing the breast cancer risk during HRT [15]. However, it should generally be noted that binding affinities, often cited in publications, can only express that there can be an action, but cannot reflect the intensity of possible action (intrinsic activity), which may be agonistic or antagonistic or only a dynamic, dose-dependent receptor-blocking process.

It therefore still remains unclear whether the observed protective estrogenic effect regarding the development of breast cancer in the WHI [4] with a significantly lower breast cancer incidence (even after 20 years of cumulative follow-up [hazard ratio 0.78; 95% confidence interval 0.65–0.93] [16]) is related to special components of the CEE mixture. Unfortunately, studies using E2 with the design of WHI have not been performed. However, studies considering this issue, at least as a secondary endpoint, suggest similar preventive effects. In the open-label, randomized controlled Danish Osteoporosis Prevention Study (DOPS), which exclusively used E2 (2 mg/day), the mortality due to breast cancer decreased significantly to about 60% (relative risk 0.38; 95% confidence interval 0.15–0.99) [17]. However, the study populations are very different, presenting healthy young women in the Danish study, in contrast to the WHI with risk factors like hypertension, smoking and obesity [3,4]. Obesity, in 40% of the study population in WHI, is an important risk factor for the development of breast cancer; that is, these women primarily have an increased risk, but a lower increase in breast cancer risk compared to the use of HRT in slim women.

In the recent 'reanalysis' from 51 epidemiological studies, the increase in breast cancer risk was significantly greater for women of lower than of higher body mass index [18]. Furthermore, the Danish women were much younger and only recently postmenopausal, in sharp contrast to the WHI. According to the 'gap hypothesis', the later start of HRT was suggested to have less breast cancer risk compared to an early start [19,20], which would suggest a higher risk for younger women. The results of the DOPS demonstrating carcinoprotective effects using E2 therefore seem to be even more remarkable.

However, decisive for the issue of breast cancer risk is not the choice of the estrogen component, but the choice of progestogen and the dependency on individual factors and the environment. We should therefore consider other activities to describe the action of the estrogen component, which have been described for both CEE and E2 in hundreds of experimental and clinical studies. The fact that several equine estrogens exhibit more powerful estrogenic effects than 17β-estradiol should not be assessed as an advantage. Increased estrogenic effects also mean, for example, greater hepatotropic actions with increased production of angiotensinogen and coagulation factors with consequently greater risk for the development of hypertension or venous thromboembolism, respectively.

Despite important studies such as the WHI or the Nurses' Health Study being performed using CEE, and many women reaping the benefits of CEE for the treatment of vasomotor symptoms or prevention of osteoporosis, from a pharmacological point of view we want to conclude that the use of CEE should no longer be considered 'up to date'. Using CEE does not meet the basic principles of clinical pharmacology! We have E2 as an alternative with the same benefits; E2 is available for transdermal application; E2 can, in contrast to CEE, be monitored in the blood to individualize the HRT and to reduce possible risks; and last but not least, the reason why we use HRT is to treat a deficit of E2, and not to treat a deficit of steroids which are only found in the urine of horses!

Choice of progestogen: primarily dependent on endometrial efficacy

The primary indication for any choice of progestogen in HRT is to achieve endometrial safety – all other properties are secondary. It is general agreement that for women with a uterus, the estrogen must be combined with a progestogen at least for 10 days, but better 12–14 days [21], in a dose which can achieve endometrial secretory transformation. For a sequential-combined combination this is mostly followed by a progestogen withdrawal bleed, and for continuous-combined combination, endometrial atrophy is achieved [22]. There has been controversy until today about the best method to monitor endometrial safety, ranging from simply observing the bleeding patterns, routinely performing ultrasound and/or endometrial histology.

In the early years, after discovering the risk of endometrial cancer induced during HRT, various *in vitro*, animal and clinical studies were performed comparing biochemical and histomorphological properties of the endometrium to compare the action of different progestogens [23–26]. For clinical use and comparison under standardized conditions, as an example the Kaufmann transformation index was defined; that is, the dose of progestogen required to achieve

secretory transformation of the endometrium primed by ethinyl estradiol (0.05 mg/day) in postmenopausal or ovariectomized women treated with the progestogen for 10 days [27].

However, these studies involved obtaining endometrial samples and are in our view not adequate for routine clinical use. To describe the different progestogenic endometrial potencies, transformation doses are often used, which are assessed in animal models, usually as the Clauberg/MacPhail transformation index; that is, testing the ability of the progestogen to transform the endometrium in rabbits [28–30]. To assess the antigonadotropic effects of progestogens in reproductive medicine, the ovulation inhibition dose is often assessed, usually in rats [14,28–30]. To combine these progestogenic property parameters, the uterotropic index was suggested, defined as the quotient of the transformation dose divided by the ovulation dose [29]. However, comparing those indices for the various progestogens which have been used repeatedly in the tables for years (e.g. [14,28–31]), we conclude that these indices can only reflect the experience from clinical practice to a limited extent, as the following examples may be able to illustrate, describing these properties for norethisterone (acetate) (NET, NETA) and dienogest (Table 5).

For NETA, the transformation dose is listed as 30–60 mg/cycle, for NET 100–150 mg/cycle. The higher dose for NET compared to NETA is striking, because if given orally in women NETA is metabolized rapidly during the gastrointestinal resorption and/or in the liver to NET. Thus, the transformation dose of NETA should be higher or at least similar to NET. However, what is even more striking is the relative high dosages for both NET and NETA, because according to endometrial biopsy studies, much lower doses can be used to achieve secretory transformed or even atrophic endometrium. For example, studies with combi-patches releasing 0.05 mg E2 and 0.250 mg NETA for sequential combination [32] ($n = 774$) or 0.025 mg E2 and 0.125 mg NETA for continuous-combined combination ($n = 50$ and $n = 379$, respectively) [33,34], performed for at least 1 year according to health authority guidelines, demonstrated endometrial safety; that is, no endometrial cancer and frequency of hyperplasia <2% (upper limit for spontaneous hyperplasia). The endometrial safety of the E2/NETA combi-patch (0.25/0.125 mg/day) was also compared to oral E2/NETA (1/0.5 mg/day) (507/169 women) with similar results showing no hyperplasia or cancer in either group [35]. From these studies, the transformation dose can be calculated to be about 3.5 mg for transdermal NETA or 15 mg for oral NETA, respectively. These doses are both lower than the transformation dose presented in Table 5 (30–60 mg), not considering the open question about the difference from NET (100–150 mg).

Table 5. Progestogenic effectivity on the endometrium (transformation dosage) and antigonadotropic effects (dose for ovulation inhibition) of different progestogens.

Progestogen	*Transformation dose (mg/cycle)*	*Ovulation inhibition dose (mg/cycle)*	*Binding affinity to PR (%)*[a]
Progesterone	4.200	300	50
Dydrogesterone	140	>30	75
MPA	50–80	10	115
CMA	20–30	1–1.7	67
CPA	20	1.0	90
NOMAC	100	5.0	125
Promegestone	10	0.5	100
NETA	30–60	0.5	–
NET	100–150	0.5	75
Dienogest	6.0	1.0	5
Drospirenone	50	2.0	35
LNG	5–6	0.05	150
Etonogestrel	2.0	0.06	150
Gestodene	3.0	0.03–0.04	90
Norgestimate	7.0	0.2	15

[a]Relative binding affinity related to promegestone = 100%.
Adapted according to Kuhl [14] and Schindler et al. [28]. CMA, chlormadinone acetate; CPA, cyproterone acetate; LNG, levonorgestrel; MPA, medroxyprogesterone acetate; NET, norethisterone; NETA, norethisterone acetate; NOMAC, nomegestrol acetate; PR progesterone receptor.

Even larger differences can be seen, for example, with dienogest. The transformation dose listed as 6 mg/cycle (Table 5) is much lower compared to the results of endometrial biopsy studies performed in postmenopausal women: we were involved in the first dose-finding study needed for the registration of E2/dienogest preparation for continuous-combined therapy testing 1 mg, 2 mg, 3 mg and 5 mg oral dienogest/day in postmenopausal women treated with 2 mg oral E2/day [36]. Based on the endometrial histology and bleeding pattern, the result was best for 3 mg dienogest/day. Because efficacy was better using 2 mg/day, E2/dienogest (2/2 mg/day) was launched, also considering follow-up studies and studies investigating endometrial efficacy for the indication of endometriosis, where efficacy was demonstrated for a 2 mg dienogest-only preparation [30,31,37–39]. Derived from these clinical studies, it must be concluded that the transformation dose for dienogest is about 60–90 mg/cycle, which is in very large contrast to the index presented in Table 5 (6 mg). This is also in contrast to the Kaufmann Index, which is assessed to be only about 0.5 mg/day for dienogest [30].

The differences shown for NET/NETA and dienogest may be explained by the fact that the Clauberg/MacPhail transformation index is assessed in rabbits, and may therefore not reflect conditions in humans. The Kaufmann Index is assessed in ovariectomized or postmenopausal women treated with ethinyl estradiol (0.05 mg/day) instead of E2 in the dosages used in HRT.

It should also be mentioned that there is only weak or even no correlation of endometrial efficacy to the relative binding affinity to the progesterone receptor assessed in different animal models (Table 5). The 15-times higher affinity of NET compared to dienogest may reflect the much stronger efficacy of NET per dose. However, the seven-times higher affinity of drospirenone compared to dienogest does not reflect the clinical situation, because both progestogens have shown similar endometrial efficacy and are consequently used at the same dose (2 mg/day). The 18-times higher affinity of CPA compared to dienogest is also striking, considering the relatively low endometrial efficacy of CPA in HRT in the dose of 1 mg/day, where we relatively often observe breakthrough bleedings.

In the 1980s, reducing the risk of endometrial cancer during HRT by performing screening using the progestogen challenge test was already recommended; that is, treating

women during 10–14 days with progestogen only to observe if there would be a progestogen-withdrawal bleed. From the correlation with large epidemiological studies evaluating the risk of endometrial cancer, it was concluded that the use of this test can reduce the risk of endometrial cancer in estrogen-treated postmenopausal women and also in premenopausal and perimenopausal women with increased endogenous estrogens [40,41]. In studies correlating the histopathology findings from endometrial biopsies with the result of challenge tests, it was concluded that the progesterone challenge test is a reliable, non-invasive, easy-to-use endometrial screening test for all postmenopausal women, and especially for high-risk groups [42,43]. The recommendation for clinical routine was that if the test is positive, ultrasonography is required to determine who requires a more accurate examination of the endometrium. If the test is negative, ultrasonography or assessment of endometrial histology is not required, because it could be expected that the endometrium is atrophic together with the observation of the maintenance of amenorrhea [42,43].

With the improvement of ultrasound diagnostic in devices and techniques, with newer possibilities of intrauterine imaging and endometrial tissue sampling (e.g. during outpatient hysteroscopy), there have been many controversial discussions about the screening value of this test [44]. However, since the establishment of our Menopause Clinic in Beijing in 2009 (first specialized menopause clinic in China, treating about 500 outpatients per day), we would like to confirm the high sensitivity and specificity of this test. Furthermore, we use routinely pretreatment with progestogen-only in women with high endometrium before we start or continue HRT, and in young women when using HRT to protect from consequences of premature ovarian insufficiency. We assess endometrial histology in unclear situations or in at-risk patients during outpatient hysteroscopy.

We mostly trust the biopsy studies; however, according to our extensive literature research as published elsewhere [22], we only found a few studies comparing the different progestogens head-to-head and almost no study comparing the progestogens in the same study population, dependent for example on weight (obesity), menopausal status, E2 levels, bleeding patterns before treatment and so on. These are all parameters which can influence the endometrial efficacy of the progestogen. Consequently, we present Table 6, which is based on our literature research [22] and clinical practice, and summarizes our recommendations regarding the choice of progestogen in terms of type and dose, especially for 'free combinations'. These are particularly necessary if using transdermal E2 (patches, gel, spray) combined with a progestogen or to treat bleeding problems by individual adaption of estrogen/progestogen dosages.

In general the progestogen dosages for sequential combination are lower compared to continuous-combined combination, because the progestogen is acting only 10, 12 or 14 days per cycle (dependent on the combined product). Individual choice of the dosage may be necessary, for example higher progestogen dosages if during sequential HRT frequent spotting occurs during the second half of the cycle (pointing to insufficient secretory transformation) or higher estrogen dosages if mid-cycle spottings are observed pointing to too weak estrogenic proliferation. These especially can be frequently seen with oral E2 in smokers due to increased hepatic metabolism of the estrogen, as we have published elsewhere **[45]**. Likewise, higher progestogen is needed, for example, in high-obese women or in cases of pre-existing endometrial hyperproliferation or endometrial

Table 6. Practical recommendations for progestogen dose for free combination with estradiol, dependent on oral or transdermal estradiol dose.

		Daily dose (according to dose of oral or transdermal E2)		
Progestogen	*Therapeutic regimen*	*Low-dose E2*[a]	*Medium-dose E2*[a]	*High-dose E2*[a]
Progesterone	Sequential	200 mg	200–300 mg	300–400 mg
(oral/preferably vaginal)	Continuous	100 mg	200 mg	300 mg
Medroxyprogesterone acetate	Sequential	5–10 mg	10–20 mg	20 mg
	Continuous	(2.5–)5 mg	5–10 mg	10 mg
Chlormadinone acetate	Sequential	2–4 mg	4 mg	4–6 mg
	Continuous	(1–)2 mg	2–4 mg	4 mg
Cyproterone acetate	Sequential	1 mg	2 mg	3–5 mg
	Continuous	1 mg	1–2 mg	2 mg
Dydrogesterone	Sequential	10 mg	10–20 mg	20 mg
	Continuous	5(–10) mg	10 mg	20 mg
Norethisterone acetate	Sequential	1 mg	1–2 mg	2 mg
	Continuous	0.5 mg	1 mg	2 mg
Dienogest	Sequential	2 mg	2–4 mg	4 mg
	Continuous	2 mg	2–4 mg	4 mg
Levonorgestrel (intrauterine)	Continuous	20 μg	20 μg	20 μg

[a]Oral estradiol: low dose, 0.5–1 mg; medium dose, 2 mg; high dose, >2 mg. CEE (only orally): low dose, 0.3/04 mg; medium dose, 0.625 mg; high dose, >0.625 mg. Transdermal estradiol (gels, patches): low dose, 25–40 μg; medium dose, 50 μg; high dose, >50 μg. Estradiol spray: low dose, one spray; medium dose, two sprays; high dose, three sprays.

All progestogens listed are administered orally in combination with oral or transdermal E2, with the exception of those combinations involving levonorgestrel (intrauterine) and vaginal progesterone. For gels, patches and spray, these are the not the dosages which are within the various available preparations. For example, gels with (according to the package insert) recommended 1.5 g (= 1500 μg!) daily application. Patches containing 3–4 mg release only about 30–50 μg estradiol into the circulation; the same applies for transdermal products. The package insert should be consulted to check what dose will actually enter the systemic circulation. With respect to the dosages in 'combi-patches' (i.e. releasing estradiol and norethisterone acetate or levonorgestrel, respectively), see text. CEE, conjugated equine estrogens; E2, estradiol.

hyperplasia pointing to antagonizing the stronger estrogenic action.

It should be mentioned that a third regime of HRT has been recommended, 'spacing out'; that is, adding the progestogen only after 2, 3 or 6 months of estrogen therapy, to reduce the total dosages of the progestogen component which may reduce the risk of breast cancer. However, an increased risk of hyperplasia and even endometrial cancer have been observed. Based on own studies [46] we can recommend this regimen only in very selected cases (clear postmenopausal, close endometrial monitoring) with progestogen dosages at least twice as presented in Table 6 for sequential therapy, also informing the patients about this 'off label' use.

In our recommendations (Table 6) we have considered the different tolerability of the various progestogens. For example, progesterone and its derivatives present a mostly higher tolerability and are mostly neutral in their metabolic and vascular effects (higher doses are possible to ensure endometrial safety) in contrast to norethisterone and its derivatives, and also considering the lower endometrial efficacy especially of progesterone with the consequence that higher doses are possible, even though this is certainly not needed in all patients. Especially high dosages of progesterone have been used in reproductive medicine (e.g. 800 mg/day) without a high frequency of side effects (with the exception of bloating due to mineralocorticoid metabolites), the strong sedative effect not being a disadvantage for HRT (if applied during evening). For the progestogen challenge test, in earlier years we often used oral NETA (1–2 mg/day) due to its strong endometrial efficacy, but in our countries this is no longer available. Alternatively, chlormadinone acetate (4–6 mg/day), dienogest (2–4 mg/day) or dydrogesterone (10 mg/day) can be recommended. For this test we would not like to recommend progesterone.

In addition to Table 6 it should be noted that for the use of transdermal E2 any 'free combination' with an oral progestogen (as presented in Table 6) can be avoided using so-called 'combi-patches'. They are available in some countries, with different dosages, releasing besides E2 also NETA or levonorgestrel (LNG) from the patch, through the skin, directly into the systemic circulation. These patches release, for example, 0.05 mg/0.25 mg E2/NETA or 0.05 mg/0.01 mg E2/LNG for sequential HRT, or 0.025 mg/0.125 mg E2/NETA, 0.030 mg/0.095 mg E2/NETA, 0.04/0.130 mg E2/NETA or 0.05/0.007 mg E2/LNG for continuous-combined HRT, applied twice per week (NETA patches) or weekly (LNG patches), respectively. Like with transdermal E2, also with the transdermal progestogen application the 'first pass' liver passage can be avoided, which is the reason why despite low dosages endometrial safety can be achieved [32–35]. Despite this reasonable concept, and despite the very strong endometrial efficacy of NETA or LNG, the combi-patches in general are rarely in use, because of frequent skin problems and also of bleeding problems, pointing to the fact that at least in some patches the progestogen dosages are too low. Thus, mostly the free combination of transdermal E2 together with an oral progestogen is used, as described in Table 6.

Open questions to the use of progesterone

It has been suggested that the gold standard of HRT should be the combination of transdermal E2 with progesterone [5,47,48]. However, its endometrial efficacy is certainly lower compared to synthetic progestogens. Because an increased risk of endometrial hyperplasia or even endometrial cancer has been observed, it was recommended to use progesterone only vaginally, which can achieve higher endometrial concentrations via vaginal–uterine circulation [49]. However, this discussion still remains controversial, considering also that a beneficial sedative effect can be achieved with oral progesterone in climacteric women [49,50]. Furthermore, it was shown in the Postmenopausal Estrogen/Progestin Interventions (PEPI) study that oral progesterone for sequential use has similar good endometrial efficacy to MPA [51]. For continuous-combined HRT, a fix combination of oral E2 and progesterone (1/100 mg) has recently been launched in the USA for the treatment of vasomotor symptoms [52], based on a study with endometrial biopsies which demonstrated sufficient progestogenic endometrial efficacy and (as expected) good efficacy, and also suggested cardiovascular safety derived from laboratory cardiometabolic markers [53,54].

However, as we have been invited to write an Editorial [55], we argued that the question of the cardiovascular risk profile needs clinical endpoint studies. Cardiovascular risks such as venous thromboembolism, stroke and coronary heart disease can be expected whenever estrogens are used orally. This new option for HRT might not replace transdermal E2 to reduce these risks. We therefore still recommend transdermal E2 plus free additional combination of oral progesterone as the 'golden standard', especially for at-risk patients. If problems occur, transdermal E2 combined with the synthetic progestogens can be prescribed according to Table 6, whereby we often use dydrogesterone in our menopause clinic. Unfortunately, we had to conclude on the basis of another review [56] that, to date, it is not possible to achieve US Food and Drug Administration-approved endometrial safety using transdermal progesterone in preparations obviously offered as gels from various pharmacies, so women have to use two different routes of administration, which can reduce compliance [56].

For any use of HRT, patients and doctors by far mostly fear the increased risk of breast cancer [57]. Independent of the route of administration, E2 combined with progesterone may present a lower increased risk of breast cancer compared with combinations using synthetic progestogens [58,59]. This should be expected if certain membrane-bound receptors which are predictive of a worse breast cancer prognosis [60,61] are expressed, as we have suggested from our *in vitro*, animal and clinical studies [62–64]. We have proposed screening for these markers to reduce at least the risk induced by one of the mechanisms for the progestogen-dependent development of breast cancer. Within an Editorial on our research, an increased expression of those markers in a larger subgroup of the study population of the WHI was discussed to be responsible for the increased breast cancer risk induced by MPA [65].

Outlook and conclusion

Besides the more 'classical pharmacological view' – that is, separating issues according to pharmacokinetics and pharmacodynamics – there are new tools, like 'pharmacogenomics', which might come to some different conclusions evaluating the action of hormones. However, regarding CEE the problem remains that due to the variability of the mixture and the necessity to consider at least 10 different components, any prediction of the net effect for the individual patient seems to be difficult or even impossible. Furthermore, it seems unlikely that the assessment from other options of pharmacological view should result in advantages over the use of the physiological hormone E2, since primarily its deficit is the reason for any use of HRT.

Besides the type of estrogen, the dosage is important, which for example should be lower in obese and in older patients. To reduce cardiovascular risks, for any HRT early initiation is most important; the concept of the 'window of opportunity' is now in general accepted. For the choice of HRT in future, we would like to predict whether it can be further verified that, if the use of progesterone can avoid the increased risk of breast cancer in contrast to (certain?) synthetic progestogens, at least in women expressing these predictive markers, the answer regarding the 'first choice' of the progestogen component will be 'progesterone', together with closer monitoring of endometrial safety. This also considers the mostly neutral metabolic and vascular effects of progesterone, which do not antagonize the estrogenic cardiovascular benefits, in contrast to synthetic progestogens such as MPA [66], the progestogen used in the WHI trial. What already seems clear is the choice of the estrogen component in cardiovascular risk patients, which should be transdermal E2.

However, as we have stressed already in our introduction, the main focus of our review is not on this combination because this has been discussed in many other recent papers. We rather wanted to add another view, with our main conclusion to choose E2 instead of CEE and regarding the progestogen component to consider in the first line the endometrial efficacy and tools for endometrial monitoring.

Limitations

There are some limitations regarding our view for the choice of HRT. First, in many countries there are significant limitations of available HRT options, which means that prescribing has to be realistic and pragmatic. Second, many women prefer oral HRT even after benefits and risks have been explained, and this should be offered as an option unless there are specific risk factors (e.g. increased risk of venous thromboembolism). As we have reported on the basis of observation of millions of patients, this risk especially in China (and maybe also in other Asian countries) is very low [67]. So still every day about 100 women in our Chinese specialized Menopause Clinic indeed get oral HRT. Third theoretical pharmacokinetics and pharmacodynamics do not always translate into the same efficacy and safety in each individual. Some individuals, for instance, do not achieve sufficient E2 levels from transdermal preparations. The significant inter-individual variation in absorption and metabolism of oral and transdermal estrogens and progestogens may not be recognized until a number of preparations have been tried in larger populations. This, however, is an important argument, to use E2 instead of CEE, progesterone instead of synthetic progestogens, because levels of the CEE components and synthetic progestogens cannot be monitored in routine practice.

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