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REVIEW

Custom-compounded bioidentical hormone therapy: why so popular despite potential harm? The case against routine use

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ABSTRACT

Wide rejection of conventional hormone therapy (HT) after the initial publication of the Women's Health Initiative (WHI) led to unjustified use of custom-compounded bioidentical hormones. In the USA, it became an unregulated drug manufacturer industry in disguise, without proper control and making false claims and misleading advertisements. Manufacturing quality is not ensured. Unspecific harm from compounding has occurred on a large scale, such as deaths from infected products and end-stage renal failure plus carcinoma due to confusion between different Chinese herbs. Oral estrogens increase venous thromboembolic and ischemic stroke events, even more when overdosed; these excess risks can be avoided by non-oral administration, readily accessible in custom-compounded HT by administering estradiol through diverse routes (of which transdermal is the best documented). Another risk specific to custom-compounded HT, resulting from estrogen/progestogen imbalance, might be excess endometrial carcinomas. HT can be optimized by continuously combining transdermal estradiol with progesterone (when required). Registered preparations do exist for such a more physiological treatment and therefore must be preferred. Custom compounding is only seldom legitimate, for example in case of allergy (such as to peanut oil) or to prescribe different combinations, doses or components (e.g. estriol, dehydroepiandrosterone or testosterone), even when not approved by local regulatory authorities despite being scientifically acceptable.

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Introduction

Misinterpretations and unwarranted generalizations of the initial results from the Women's Health Initiative (WHI) trial of conjugated equine estrogens + medroxyprogesterone acetate (CEE + MPA)[1] engendered a drive towards uncontrolled use of custom-compounded bioidentical hormones. Indeed, subsequent disinformation against hormone therapy (HT) by the lay press has created a favorable opening for propagation of the concept that 'bioidentical hormones are safer and/or even more effective/reliable than traditional HT'.

The term 'bioidentical hormones' means just that they have the same molecular structure as the endogenous hormones present in the human body. Although the term 'bioidentical' seems more like a marketing than a scientific or medical term, it continues to be widely used despite a proposal by the editors of *Climacteric* to replace it by 'body-identical'[2].

Custom-compounded hormones: a thriving business. Why?

The increasing rush towards custom-compounded hormones is an indirect proof that menopausal hormone therapy (MHT) is irreplaceable for managing climacteric symptoms such as hot flushes and vaginal dryness. Admittedly, an important placebo effect has been evidenced, explaining why numerous alternative treatments, such as phytoestrogens, can somewhat improve clinical symptoms but have not been shown to be superior to placebo[3]. But, after the WHI, far too many women refused or were denied an appropriate MHT. Besides altering well-being, avoiding MHT comes at a considerable economic cost to themselves and to society[4] and results in excess mortality[5]. It is noteworthy that women with moderate to severe vasomotor symptoms have lower bone mineral density (BMD) and increased hip fracture rates[6], while the efficiency of MHT in the prevention and treatment of osteoporotic fractures always remained undisputed[7].

Women clearly need and request efficient care for their climacteric symptoms. But, in the USA, many women no longer trust therapies approved by the Food and Drug Administration (FDA) and consider them as dangerous drugs; 25–42% of MHT users even consider that custom-compounded hormones (CCH) are more safe[8]. A significant proportion of North American pharmacists share similar misconceptions[9], believing in the safety of CCH, even conferring them a greater confidence. Moreover, at least in the USA, many practitioners are even unaware that bioidentical hormones do exist as FDA-approved products[10].

In the USA, the business of CCH has increased tremendously and has almost become an unregulated industry; compounding pharmacies are now making, without proper

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control by authorities, (multi)billion dollars each year[11] and this amount is still increasing[12]. This problem, however, is mostly limited to North America since pharmacy compounding is not used on such a large scale in most other countries, such as in Europe.

Though all scientific societies, as well as regulatory authorities, still claim that bioidentical hormones have not been scientifically proven to be safer than (most) registered hormones, the scientific literature is full of papers highly suggesting the very likely superiority of an optimized MHT combining micronized progesterone and transdermal/percutaneous estradiol, as previously reviewed[13,14]. A randomized, controlled trial (RCT) of such optimal MHT versus placebo is still missing but is unlikely ever to be conducted, particularly given its expense. However, until such a desired RCT is completed, it is reasonable to base daily clinical practice (and even issue strong recommendations[15]) on data of moderate-to-low levels of evidence, especially from the available observational studies[16]. Some epidemiologists and statisticians have shown that the estrogen + progestin (E/P) WHI study was not exempt from bias[17] and even had become observational[18,19]. In 2010, the US Endocrine Society[16] indeed downgraded the quality of many WHI conclusions to level B (moderate-quality evidence), although recognizing that it remained the best available evidence.

Previous misinterpretations and unwarranted generalizations

We consider that regulatory authorities and, to some extent, scientific societies, bear the responsibility in this 'marketed' drive by the lay press and wellness physicians towards custom-compounded hormones, by endorsing class effects, misinterpretations and unwarranted generalizations. They should have emphasized the minor clinical relevance of absolute risks of the order of <5 per 10 000 per year, as well as the impossibility to discriminate among bias, confounding and causation when relative risks are less than 1.5. Instead of insisting on lack of scientific proof, they should have quickly promoted MHT optimization rather than banning MHT for more than 2–3 years, even for recently menopausal symptomatic women. This is now on the way to be corrected[20,21], even by lead WHI investigators who, after more than a decade of wandering, recognize some of their recommendations as having been wrong and advocate 'getting clinical care back on track'[22].

Early vs. late initiation of menopausal hormone therapy

One generalization has come from the confusion between MHT initiation before 60 years of age (or less than 10 years after menopause) and MHT initiation beyond. In the latter situation, WHI studies indeed suggested cardiovascular harm from MHT, while conclusively suggesting that MHT may be beneficial when initiated near menopause[23]. The validity of the hypothesis of 'early cardiovascular benefit – late cardiovascular harm', commonly named 'window of opportunity', has recently been validated in the DOPS (Danish Osteoporosis Prevention Study)[24] and ELITE (Early versus Late Initiation Trial with Estradiol)[25], as well as by the last Cochrane review[26], in accordance with the 2009 meta-analysis of Salpeter and colleagues[27].

Continuation of menopausal hormone therapy

Another undue generalization was to state that continuation of MHT initiated near menopause bears similar cardiovascular harms as MHT initiated 'too' late, since it is not warranted by any conclusive data. In fact, in the last revision of the Cochrane review (solely considering RCTs), there was high-quality evidence that it had little effect on death or coronary heart disease (CHD), even in those who started MHT more than 10 years after menopause, despite increased rates of venous thromboembolism and stroke[26].

Duration of climacteric symptoms

Moreover, the usual duration of moderate to severe vasomotor symptoms had been severely underestimated: the average duration is 7.4 years and more than one-third of symptomatic women continue to suffer vasomotor symptoms for more than 10 years after their final menstrual period[28]. Therefore, the dogma to systematically stop MHT at 60 or 65 years of age has become obsolete[29,30]: symptomatic women may and should be allowed to extend use of the most effective treatment, though at the lower effective dose and after assessing their risk–benefit ratio.

Harms from discontinuation of menopausal hormone therapy

MHT discontinuation again leads to an increased hip fracture risk within 2 years[31]. A cross-sectional database analysis from Finland also showed transient 1-year increased cardiac and stroke deaths (though only in women aged less than 60 at either initiation or discontinuation of MHT)[32]. Such harm soon after MHT withdrawal is consistent with comparable results observed in three previous RCTs, as reviewed by Pines[33]. In the Finnish cohort[34], there was even a linear relationship between cardiovascular benefit and duration of estrogen exposure, even in women older than 60.

Non-specific risks of custom-compounding

For some patients, CCH are really useful for better flexibility of dosing or formulation or for allergen avoidance. An example is that of peanut allergy: registered micronized progesterone preparations originally contained peanut oil, making their intake dangerous for allergic subjects. However, between 2004 and now, the laboratory has progressively replaced peanut oil by sunflower oil in most countries, except in the USA where sunflower oil is not authorized by the FDA in drugs but only in the food industry. Therefore, in countries where registered micronized progesterone still contains peanut oil, it is entirely legitimate to compound progesterone for those allergic patients.

Though the majority of compounding pharmacies are dedicated to providing high-quality products, they cannot

totally rule out some undesirable events. One proven risk is that of contamination by viruses, bacteria or other pathogens. For example, a well-documented large series of fungal infections (especially meningitis) has been associated with injections of a contaminated glucocorticoid from a single compounding pharmacy[35]. Among 13 534 potentially exposed cases, there occurred significant morbidity and mortality (at least 61 deaths)[36].

Another proven risk concerns purity and thus absence of harmful contaminants. Thus, in the compounding of Chinese herbs for weight reduction, a manufacturing error led to substitution of the intended herb (*Stephania tetrandra*) by another (*Aristolochia fangchi*) which is nephrotoxic and carcinogenic. It resulted in rapidly progressive renal failure towards end-stage renal disease in 43 Belgian patients, with additionally a high prevalence of urothelial carcinoma[37]. This specific problem can still occur world-wide since these botanical remedies remain available through the internet[38].

Custom-compounded preparations may also contain undesirable additives or preservatives, degradation products, process impurities, residual solvents, bacterial endotoxins or residual amounts of other drugs made in the same facility: all can induce more or less serious side-effects.

Legal control and regulatory situations of custom compounding vary greatly from country to country and thus will not be considered here. The situation in the USA is quite peculiar since there really was until recently a legal flaw in this country[39,40]. It has allowed the emergence of large compounding pharmacies, which just have become drug manufacturers in disguise, without properly enforced standards of good manufacturing, quality controls and monitoring. They are compounding bulk volumes of drugs prior to and in anticipation of the receipt of a valid prescription, use false and misleading advertising, and do not provide any proper documentation leaflets for both physician and patient.

MHT and endometrial cancer

Opposed vs. unopposed MHT

As universally agreed, unopposed estrogen bears an increased risk of endometrial cancer, even more in normal-weight women (body mass index (BMI) $< 25\ kg/m^2$). This risk remains elevated for at least 10 years since last use of estrogen[41]. As summarized in a Cochrane review[42], there are both dose– and duration–response relationships between unopposed estrogen and risk of endometrial hyperplasia, susceptible to lead to cancer. The risks are significantly reduced by adding a progestogen for at least 10 days per cycle (or month), the protection being greater the more days every month that progestogen is added to estrogen[43,44]. High relative risks of endometrial cancer have been evidenced in long-cycle E/P users (progestogen given only once for 10–14 days at the end of a 3-month estrogen administration)[45]: 1.63 (95% confidence interval (CI) 1.12–2.38) for >5 years use, up to 2.95 (95% CI 2.40–3.62) for >10 years. It thus further emphasizes the importance of a proper E/P balance. Though most studies showed some protection against endometrial cancer by sequential E/P use, a 2005 meta-analysis[43] anyway indicated an overall residual increased relative risk of 1.14 (95% CI 1.01–1.28). Moreover, cyclic E/P even increased endometrial cancer risk during short-term use (< 2 years) in a very large Danish nationwide prospective cohort utilizing national registers[46]. Table 1, adapted from a 2014 meta-analysis[44], clearly shows the different protective effects of different lengths of sequential progestogen use; in contrast, continuous combined E/P (either for at least 25 days per cycle or non-stop) leads to lower endometrial cancer risk than placebo[44,45,47], especially among heavier women (BMI $>30\ kg/m^2$). Several (but not all[48]) long-term observational studies showed that sequential E/P unfortunately became less protective after 5–10 years use[45,47,49], while continuous combined E/P use remained exempt from increased endometrial cancer risk for up to 10 years, though possibly less afterwards (Table 2). In the Danish cohort, this protection surprisingly occurred essentially for type II endometrial cancer (which is less hormone-dependent)[46].

Table 1. Relative risk of endometrial cancer from estro-progestogen menopausal hormone therapy according to progestogen administration schedule (sequential or continuous combined). Adapted from the meta-analysis of Brinton and Felix (*J Steroid Biochem Mol Biol* 2014;142:83–9).

Regimen	*Progestogen schedule*	*Relative risk (95% confidence interval)*
Sequential	<10 days/month	1.76 (1.51–2.05)
	10–24 days/month	1.07 (0.92–1.24)
Continuous combined	At least 25 days/month	0.78 (0.72–0.86)

The case of estriol

Estriol cannot be converted back to other estrogens and has a lower affinity for and a shorter binding time to estrogen receptors α predominant in endometrium (only 10% of

Table 2. Relative risk of endometrial cancer from estro-progestogen menopausal hormone therapy according to progestogen administration schedule (sequential, short or long or continuous combined) and duration. Adapted from Jaakkola *et al.* (*Int J Cancer* 2011;128:1644–51), Doherty *et al.* (*AJOG* 2007;197:139–47) and Trabert *et al.* (*Int J Cancer* 2013;132:417–26).

		Relative risk (95% confidence interval)		
Treatment regimen	*Duration (years)*	*Jaakkola et al. (2011)*	*Doherty et al. (2007)*	*Trabert et al. (2013)*
Sequential (10–24 days/month)	<5	0.67 (0.52–0.86)		NA
	5+		2.0 (1.2–3.5)	
	>10	1.38 (1.15–1.66)		1.88 (1.36–2.60)
Continuous combined	<5	0.45 (0.27–0.73)		NA
	<10	NA		0.53 (0.39–0.73)
	5+		0.77 (0.45–1.3)	
	9+		0.62 (0.31–1.3)	
	>10	0.79 (0.61–1.02)		0.98 (0.63–1.54)

NA, not available

binding affinity of estradiol) and breast tissues. Estriol failed to stimulate true uterine growth[50] unless given at very high doses or by repetitive intake: some endometrial effect indeed has been evidenced by administering 2 mg estriol three times a day[51]. Of dubious clinical efficacy for most climacteric symptoms with the exception of its proven activity on the cervico-vaginal and lower urinary tract mucosa (via a strong binding affinity to vaginal estrogen receptors β), it thus has usually been considered as devoid of any systemic effect. It therefore has been considered that addition of a progestogen is unnecessary. However, among users of oral estriol (1–2 mg/daily), endometrial cancer risk has not been adequately quantified in epidemiological studies. Though several observational studies were reassuring (such as the study by Granberg and colleagues and other studies cited in their paper[52]), a single nationwide, population-based, case–control study in Sweden[53] reported a duration-related increased endometrial cancer risk in oral but not in vaginal estriol users, despite higher blood levels when vaginally administered; strangely also, the excess relative risk was lost rapidly after treatment cessation. Nevertheless, estriol use in oral CCH preparations should best be avoided.

The risk of endometrial cancer from custom-compounded hormones

CCH are administered through a variety of delivery modes, including orally and through the skin (cream, gel, patch, spray, lotion, etc.). Since the excipient influences the pharmacokinetics, it results in varied absorption profiles and 24-h areas under the curve (AUC). For example, in a RCT[54], the estradiol AUC was 80% lower with the CCH preparation than with an FDA-approved one. But for estradiol delivery, many approved gels and patches do exist that have been proven to be efficient, and their transdermal delivery is relatively consistent in a time-release fashion close to a continuous secretion.

As overviewed, underdosing or overdosing is not only a possibility but has been demonstrated by official evaluations[39]: analyzed for their E/P content, many CCH preparations exhibited an imbalanced proportion of these two components, with often more estradiol but less progesterone than intended, thus potentially increasing endometrial cancer risk; furthermore, the endometrial safety of the hormonal ratios prescribed was never evaluated.

As a matter of fact, scientists indeed suspect that wide use of CCH is associated with greater occurrence of endometrial cancer than expected: several cases have been reported[55–57] that could be considered as the 'canary in the coal mine'. Moreover, in a small survey by the NAMS (North American Menopause Society), there were four cases of endometrial cancer among 326 users of CCH compared to none among the 738 users of FDA-approved MHT[8], besides a higher rate of vaginal bleeding. It thus supports the likely occurrence of more endometrial cancer with CCH.

The case of progesterone

With oral progesterone (the progestogen most used in CCH), compliance could be a critical issue due to its shorter half-life than all other progestogens. It could allow temporary or partial withdrawal of the antagonistic effect of the progestogen upon the proliferative effect of estrogen. Nevertheless, in the Postmenopausal Estrogen/Progestin Interventions (PEPI) trial (an old RCT that also tested use of oral micronized progesterone), histology showed consistent endometrial protection over 3 years in women given daily 0.625 mg CEE + sequentially 200 mg micronized progesterone for 12 days, in comparison to placebo[58]. Similarly the 4-year KEEPS (Kronos Early Estrogen Prevention Study) RCT[59] did not find any significant difference in endometrial cancer rates between users of placebo or MHT (at similar doses and regimen). There are only few data regarding other doses and schedules of oral administration of micronized progesterone. One small trial (30 participants) over 4 months of continuous combined administration for 25 days per month of daily 2 mg estradiol + micronized progesterone showed an atrophic endometrium in most women receiving daily 100 (even 50) mg micronized progesterone and in all women receiving 200 mg[60].

Though control of endometrial glandular mitosis (and thus proliferation inhibition) is achieved with lower progesterone doses than actually necessary for secretory changes (to be achieved when progestogen is added sequentially after endometrial proliferation during the first, estrogen-only phase)[61], endometrial protection cannot be assessed on the basis of blood progesterone concentrations but only upon endometrial histology[62]. This makes completely useless any attempt to individually titrate the dose on the basis of hormonal concentrations in any accessible fluid such as blood or saliva.

In France, the only country in which micronized progesterone has been used on a large scale for several decades in association with estradiol, there does not exist any fixed registered combination of both; therefore, the patient is obliged carefully to follow instructions to add 200 mg micronized progesterone for 12–14 days each month and must use two separate medications (daily two pills or one pill + the gel or one pill daily + a patch once or twice weekly), without any proper memory aid calendar. Not surprisingly, the result is poor compliance. The adherence is probably better with the late introduction by the company of a fixed continuous combined regimen, for 25 days per month, of simultaneous estradiol +100 mg micronized progesterone, though still requiring use of two separate medications. Besides, French women on the whole are leaner than those in the USA and thus more sensitive to unopposed estrogen and thus to unsatisfactory sequential treatments. This is one likely explanation why, in the European Prospective Investigation into Cancer (EPIC) cohort study, more cases of endometrial cancer were observed in women receiving estradiol + micronized progesterone (though on the basis of small numbers)[63]. As discussed by Gompel and Santen[64], the ensuing claimed possible inferiority of progesterone, compared to other progestogens, bears only weak plausibility and is probably the result of confusing bias (mostly since many women used it more or less properly, resulting in an approximate sequential regimen). This issue has not been correctly taken into account in a recent systematic review[65], wrongfully

claiming that micronized progesterone increases risk of endometrial cancer regardless of regimen, without any proper reference to the PEPI trial. In contrast, another concomitant systematic review[66] underscores pertinent criticisms (several biases of different types) of the cohort studies reporting an increased risk of endometrial cancer when using micronized progesterone to oppose estrogen. One criticism concerns the inclusion of women who successively used different types and regimens of progestogen; another pertains to unawareness of regimen (sequential or continuous), whether being total (in the French Etude épidémiologique de Femmes de la Mutuelle Générale de l'Education Nationale (E3N) cohort of EPIC) or partial (39% in EPIC).

Transdermal progesterone

The use of transdermal progesterone is a crucial issue since only about 10% of what is topically delivered through water-based gel or cream is detected in serum, while capillary blood levels are approximately 100-fold greater[67]. It suggests that tissue exposure might be greater than currently admitted, possibly through lymphatic delivery. Alcohol-based creams or gels, however, result in higher blood concentrations[62]. Anyhow, it is widely admitted that topical progesterone is unsuitable for endometrial protection[68,69], since the very scarce available data failed to show any endometrial protection from progesterone creams or gels. An increased endometrial cancer risk thus could result from transdermal progesterone delivery combined with estradiol in CCH therapy.

Efficacy of custom-compounded hormones

Estradiol

A recent Cochrane review (solely considering RCTs) attempted to compare with placebo the effectiveness on vasomotor symptoms of bioidentical hormones (in fact solely unopposed estradiol, probably not resulting from custom compounding); it concluded, with low to moderate evidence, that estradiol (administered orally or as patch, gel, topical emulsion or intranasally) is better than placebo[70]. No other firm conclusion was possible.

No satisfactory trial has attempted to demonstrate the efficacy of CCH. Nevertheless, when estradiol or E/P is prescribed for vasomotor complaints, one can judge the effect upon symptom relief, even if a placebo effect cannot be ruled out. On the other hand, a clinical effect can be reached at the price of overdosing, with possible serious harm (such as unnecessarily increased events of venous thromboembolism, ischemic stroke and endometrial cancer).

Dehydroepiandrosterone

Dehydroepiandrosterone (DHEA), a precursor of sex steroids, represents a large reservoir for intracellular conversion to androgen and estrogen in non-reproductive tissues; it thus could theoretically exert some favorable clinical effects. Hence, it is frequently prescribed in CCH despite the lack of evidence for any clinically significant effect when given orally or systemically. Though conflicting results have been reported, a review and meta-analysis concluded that oral DHEA does not significantly impact libido and sexual function in postmenopausal women with normal adrenal function, the only significant benefit residing in a small change in lumbar spine BMD[71]. A similar previous review did not find any benefit on well-being and cognitive performance[72]. It contrasts with the finding that DHEA sulfate levels are associated, in women aged 21–77 years, with more favorable cognitive function[73], and that lower DHEA sulfate levels are linked with higher cardiovascular and all-cause mortality[74]. In conclusion, oral DHEA, probably devoid of any deleterious effect, can probably merely serve as a placebo in CCH, though possibly converted in very tiny amounts to estrogens and androgens.

Testosterone

Endogenous androgens play some physiological role (especially for libido) in women. Testosterone levels decline progressively with age, starting in the premenopausal years. It thus could seem attractive to prescribe testosterone to postmenopausal women. As reviewed[75], a disorder (referred to as female hypoactive sexual desire disorder) has been described that somewhat responds to testosterone administration through a transdermal patch daily delivering 300 µg. Scientific societies recommend restricting testosterone use to women with sexual dysfunction due to such a syndrome[76] and against prescribing testosterone to any woman with so-called androgen deficiency. Long-term safety data are lacking. Some favorable effects on bone and muscle have been reported. Serious androgenization side-effects may occur but are somewhat avoidable by using formulations and doses appropriate for women. In most countries, approved testosterone drugs for use in women are lacking and therefore it is often prescribed off-label as well as in up to 40% of CCH prescriptions[77]; it is possible that most of these are illegitimate.

Conclusion

In the context of mistrust towards traditional MHT and of suggestion of safer MHT with 'natural' hormones given more physiologically, it is not surprising that patients and doctors have purposely turned towards 'body-identical' hormones and non-oral administration. Unfortunately, it has led to widespread and unjustified use of custom-compounded bioidentical hormones rather than registered, approved products. Custom-compounding inherently bears potential risks for the patient related to a general lack of standardization and quality control. These risks (such as morbidity and deaths from contamination) indeed have happened in real life, amplified by preparing and delivering custom-compounded hormones on a very large scale, mimicking industrial production (but without proper control). Inconsistencies in the compound preparations have been documented: oral estradiol

overdosing may result in excess venous thromboembolism and E/P imbalance may result in an excess of endometrial cancers, the latter indeed being suspected due to several reports.

A comprehensive overview of compounded bioidentical hormones in practice appeared recently as an Endocrine Society scientific statement[78]. Approved, registered, bioidentical hormonal drugs that are produced in monitored facilities are widely available. Therefore, it is entirely unnecessary to switch to custom-compounded hormone therapy, proven to be (potentially) more harmful. Therefore, when registered products are available, they should always be used in the first place.

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References

1. WHI Writing Group. Risks and benefits of estrogen plus progestin in healthy postmenopausal women. *JAMA* 2002;288:321–33
2. Panay N, Fenton A. Bioidentical hormones: what is all the hype about? *Climacteric* 2010;13:1–3
3. Roberts H, Lethaby A. Phytoestrogens for menopausal vasomotor symptoms: a Cochrane review summary. *Maturitas* 2014;78:79–81
4. Fenton A, Panay N. Menopause: quantifying the cost of symptoms. *Climacteric* 2013;16:405–6
5. Sarrel P, Njike V, Vinante V, Katz D. Mortality toll of estrogen avoidance: an analysis of excess deaths among hysterectomized women aged 50 to 59 years. *Am J Public Health* 2013;103:1583–8
6. Crandall CJ, Aragaki A, Cauley JA, *et al*. Associations of menopausal vasomotor symptoms with fracture incidence. *J Clin Endocrinol Metab* 2015;100:524–34
7. Zhu L, Jiang X, Sun Y, Shu W. Effect of hormone therapy on the risk of bone fractures: a systematic review and meta-analysis of randomized controlled trials. *Menopause* 2015;23:461–70
8. Gass MLS, Stuenkel CA, Utian WH, LaCroix A, Liu JH, Shifren JL. Use of compounded hormone therapy in the United States: report of the North American Menopause Society Survey. *Menopause* 2015;22:1276–84
9. Siyam T, Yuksel N. Beliefs about bioidentical hormone therapy: a cross-sectional survey of pharmacists. *Maturitas* 2013;74:196–202
10. Files JA, Kransdorf LN, Ko M, *et al*. Bioidentical hormone therapy: an assessment of provider knowledge. *Maturitas* 2016;94:46–51
11. Pinkerton JV, Santoro N. Compounded bioidentical menopausal hormone therapy: identifying use trends and knowledge gaps among US women. *Menopause* 2015;22:926–36
12. Pinkerton JV, Constantine GD. Compounded non-FDA-approved menopausal hormone therapy prescriptions have increased: results of a pharmacy survey. *Menopause* 2016;23:359–67
13. L'Hermite M, Simoncini T, Fuller S, Genazzani AR. Could transdermal estradiol + progesterone be a safer postmenopausal HRT? A review. *Maturitas* 2008;60:185–201
14. L'Hermite M. HRT optimization, using transdermal estradiol plus micronized progesterone, a safer HRT. *Climacteric* 2013;16(Suppl 1):44–53
15. Mohammed K, Murad MH. Response to the Letter: "Transdermal vs oral estrogen therapy and venous thromboembolism: upgrade the level of evidence" by Scarabin MC, *et al*. *J Clin Endocrinol Metab* 2016;101:L32
16. Santen RJ, Allred DC, Ardoin SP, *et al*. Postmenopausal hormone therapy: an Endocrine Society scientific statement. *J Clin Endocrinol Metab* 2010;95(Suppl 1):S1–S66
17. Shapiro S. Risk of breast cancer among users of estrogen plus progestogen and unopposed estrogen: is the likelihood of bias symmetrical? *Climacteric* 2015;18:333–5
18. Shapiro S, Farmer RDT, Mueck AO, Seaman H, Stevenson JC. Does hormone replacement therapy cause breast cancer? An application of causal principles to three studies: part 2. The Women's Health Initiative: estrogen plus progestogen. *J Fam Plann Reprod Health Care* 2011;37:165–72
19. Shapiro S, de Villiers TJ, Pines A, *et al*. Risks and benefits of hormone therapy: has medical dogma now been overturned? *Climacteric* 2014;17:215–22
20. Stuenkel CA, Davis SR, Gompel A, *et al*. Treatment of symptoms of the menopause: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2015;100:3975–4011
21. Baber RJ, Panay N, Fenton A. and the IMS Working Group. 2016 IMS Recommendations on women's midlife health and menopause hormone therapy. *Climacteric* 2016;19:109–50
22. Manson JE, Kaunitz AM. Menopause management: getting clinical care back on track. *N Engl J Med* 2016;374:803–6
23. Rossouw JE, Prentice RL, Manson JE, *et al*. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. *JAMA* 2007;297:1465–78
24. Schierbeck LL, Rejnmark L, Tofteng CL, *et al*. Effect of hormone replacement therapy on cardiovascular events in recently postmenopausal women: randomised trial. *Br Med J* 2012;345:e6409
25. Hodis HN, Mack WJ, Henderson VW, *et al*. Vascular effects of early versus late postmenopausal treatment with estradiol. *N Engl J Med* 2016;374:1221–31
26. Boardman H, Hartley L, Eisinga A, *et al*. Hormone therapy for preventing cardiovascular disease in post-menopausal women. *Cochrane Libr* 2015;3:1–160
27. Salpeter SR, Cheng J, Thabane L, Buckley NS, Salpeter EE. Bayesian meta-analysis of hormone therapy and mortality in younger postmenopausal women. *Am J Med* 2009;122:1016–22
28. Freeman EW, Sammel MD, Sanders RJ. Risk of long-term hot flashes after natural menopause: evidence from the Penn Ovarian Aging Study cohort. *Menopause* 2014;21:924–32
29. ACOG Committee Opinion No 556. Hormone therapy and heart disease. *Obstet Gynecol* 2013;565:1407–10
30. Gass MLS, Maki PM, Shifren JL, *et al*. NAMS supports judicious use of systemic hormone therapy for women aged 65 years and older. *Menopause* 2015;22:685–6
31. Karim R, Dell RM, Greene DF, Mack WJ, Gallagher JC, Hodis HN. Hip fracture in postmenopausal women after cessation of hormone therapy: results from a prospective study in a large health management organization. *Menopause* 2011;18:1172–7
32. Mikkola TS, Tuomikoski P, Lyytinen H, *et al*. Increased cardiovascular mortality risk in women discontinuing postmenopausal hormone therapy. *J Clin Endocrinol Metab* 2015;100:4588–94
33. Pines A. Withdrawal of hormone therapy and increased risk of cardiovascular disease. *Climacteric* 2016;19:249–51
34. Mikkola TS, Tuomikoski P, Lyytinen H, *et al*. Estradiol-based postmenopausal hormone therapy and risk of cardiovascular and all-cause mortality. *Menopause* 2015;22:976–83
35. Smith RM, Schaefer MK, Kainer MA, *et al*. Fungal infections associated with contaminated methylprednisolone injections. *N Engl J Med* 2013;369:1598–609
36. Chiller TM, Roy M, Nguyen D, *et al*. Clinical findings for fungal infections caused by methylprednisolone injections. *N Engl J Med* 2013;369:1610–19
37. Nortier J, Muniz Martinez M-C, Schmeiser H, *et al*. Urothelial carcinoma associated with the use of a chinese herb (Aristolochia Fangchi). *N Engl J Med* 2000;342:1686–92
38. Debelle FD, Vanherweghem J-L, Nortier JL. Aristolochic acid nephropathy: a worldwide problem. *Kidney Int* 2008;74:158–69
39. Pinkerton JV, Pickar JH. Update on medical and regulatory issues pertaining to compounded and FDA-approved drugs, including hormone therapy. *Menopause* 2016;23:215–23
40. Simon JA. The Woman's Health Initiative and one of many unintended consequences. *Menopause* 2016;23:1057–9

41. Lacey JV, Brinton LA, Lubin JH, Sherman ME, Schatzkin A, Schairer C. Endometrial carcinoma risks among menopausal estrogen plus progestin and unopposed estrogen users in a cohort of postmenopausal women. *Cancer Epidemiol Biomarkers Prev* 2005;14:1724–31
42. Roberts H, Hickey M, Lethaby A. Hormone therapy in postmenopausal women and risk of endometrial hyperplasia: a Cochrane review summary. *Maturitas* 2014;77:4–6
43. Beral V, Bull D, Reeves G. Endometrial cancer and hormone-replacement therapy in the Million Women Study. *Lancet* 2005;365:1543–51
44. Brinton LA, Felix AS. Menopausal hormone therapy and risk of endometrial cancer. *J Steroid Biochem Mol Biol* 2014;142:83–9
45. Jaakkola S, Lyytinen HK, Dyba T, Ylikorkala O, Pukkala E. Endometrial cancer associated with various forms of postmenopausal hormone therapy: a case control study. *Int J Cancer* 2011;128:1644–51
46. Mørch LS, Kjær SK, Keiding N, Løkkegaard E, Lidegaard Ø. The influence of hormone therapies on type I and II endometrial cancer: A nationwide cohort study. *Int J Cancer* 2016;138:1506–15
47. Trabert B, Wentzensen N, Yang HP, *et al*. Is estrogen plus progestin menopausal hormone therapy safe with respect to endometrial cancer risk? *Int J Cancer* 2013;132:417–26
48. Phipps AI, Doherty JA, Voigt LF, *et al*. Long-term use of continuous-combined estrogen-progestin hormone therapy and risk of endometrial cancer. *Cancer Causes Control* 2011;22:1639–46
49. Doherty JA, Cushing-Haugen KL, Saltzman BS, *et al*. Long-term use of postmenopausal estrogen and progestin hormone therapies and the risk of endometrial cancer. *Am J Obstet Gynecol* 2007;197:12–14
50. Anderson J, Peck E, Clark S. Estrogen-induced uterine responses and growth: relationship to receptor estrogen binding by uterine nuclei. *Endocrinology* 1975;96:160–7
51. Englund D, Johansson E. Endometrial effect of oral estriol treatment in postmenopausal women. *Acta Obstet Gynecol Scand* 1980;59:449–51
52. Granberg S, Eurenius K, Lindgren R, Wilhelmsson L. The effects of oral estriol on the endometrium in postmenopausal women. *Maturitas* 2002;42:149–56
53. Weiderpass E, Baron JA, Adami H-O, *et al*. Low-potency oestrogen and risk of endometrial cancer: a case-control study. *Lancet* 1999;353:1824–8
54. Sood R, Warndahl RA, Schroeder DR, *et al*. Bioidentical compounded hormones: a pharmacokinetic evaluation in a randomized clinical trial. *Maturitas* 2013;74:375–82
55. Eden JA, Hacker NF, Fortune M. Three cases of endometrial cancer associated with "bioidentical" hormone replacement therapy. *Med J Aust* 2007;187:244–5
56. Jessel R, Nachtigall M, Nachtigall L. Two cases of endometrial adenocarcinoma in postmenopausal women on bioidentical hormone replacementtherapy. *Menopause* 2009;16:1247 (poster 23)
57. Davis R, Batur P, Thacker HL. Risks and effectiveness of compounded bioidentical hormone therapy: a case series. *J Womens Health (Larchmt)* 2014;23:642–8
58. Writing Group for the PEPI trial. Effects of hormone replacement therapy on endometrial histology in postmenopausal women. The Postmenopausal Estrogen/Progestin Interventions (PEPI) trial. *JAMA* 1996;275:370–5
59. Harman SM, Black DM, Naftolin F, *et al*. Arterial imaging outcomes and cardiovascular risk factors in recently menopausal women: a randomized trial. *Ann Intern Med* 2014;161:249–60
60. Darj E, Nilsson S, Axelsson O, Hellberg D. Clinical and endometrial effects of oestradiol and progesterone in post-menopausal women. *Maturitas* 1991;13:109–15
61. Moyer D, de Lignières B, Driguez P, Pez J. Prevention of endometrial hyperplasia by progesterone during long-term estradiol replacement: influence of bleeding pattern and secretory changes. *Fertil Steril* 1993;59:992–7
62. Stanczyk FZ. Treatment of postmenopausal women with topical progesterone creams and gels: are they effective? *Climacteric* 2014;17(Suppl 2):8–11
63. Allen NE, Tsilidis KK, Key TJ, *et al*. Menopausal hormone therapy and risk of endometrial carcinoma among postmenopausal women in the European Prospective Investigation into cancer and nutrition. *Am J Epidemiol* 2010;172:1394–403
64. Gompel A, Santen RJ. Hormone therapy and breast cancer risk 10 years after the WHI. *Climacteric* 2012;15:241–9
65. Sjögren L, Mørch L, Lokkegaard E. Hormone replacement therapy and the risk of endometrial cancer: a systematic review. *Maturitas* 2016;91:25–35
66. Stute P, Neulen J, Wildt L. The impact of micronized progesterone on the endometrium: a systematic review. *Climacteric* 2016;19:316–28
67. Du J, Sanchez P, Kim L, Azen C. Percutaneous progesterone delivery via cream or gel application in postmenopausal women: a randomized cross-over study of progesterone levels in serum, whole blood, saliva, and capillary blood. *Menopause* 2013;20:1–7
68. Wren BG, McFarland K, Edwards L, *et al*. Effect of sequential transdermal progesterone cream on endometrium, bleeding pattern, and plasma progesterone and salivary progesterone levels in postmenopausal women. *Climacteric* 2000;3:155–60
69. Gambrell R. Progesterone skin cream and measurements of absorption. *Menopause* 2003;10:2–3
70. Gaudard A, Silva D, Souza S, Puga M, *et al*. Bioidentical hormones for women with vasomotor symptoms. *Cochrane Database Syst Rev* 2016;8:1–103
71. Elraiyah T, Sonbol MB, Wang Z, *et al*. Clinical review: The benefits and harms of systemic dehydroepiandrosterone (DHEA) in postmenopausal women with normal adrenal function: a systematic review and meta-analysis. *J Clin Endocrinol Metab* 2014;99:3536–42
72. Davis SR, Panjari M, Stanczyk FZ. Clinical review: DHEA replacement for postmenopausal women. *J Clin Endocrinol Metab* 2011;96:1642–53
73. Davis SR, Shah SM, McKenzie DP, Kulkarni J, Davison SL, Bell RJ. Dehydroepiandrosterone sulfate levels are associated with more favorable cognitive function in women. *J Clin Endocrinol Metab* 2008;93:801–8
74. Shufelt C, Bretsky P, Almeida CM, *et al*. DHEA-S levels and cardiovascular disease mortality in postmenopausal women: results from the National Institutes of Health, National Heart, Lung, and Blood Institute (NHLBI)-sponsored Women's Ischemia Syndrome Evaluation (WISE). *J Clin Endocrinol Metab* 2010;95:4985–92
75. Davis SR, Worsley R. Androgen treatment of postmenopausal women. *J Steroid Biochem Mol Biol* 2014;142:107–14
76. Wierman ME, Arlt W, Basson R, *et al*. Androgen therapy in women: a reappraisal: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2014;99:3489–510
77. Richardson M. Bioidentical hormone therapy: a challenge for the menopause clinician. *Menopause* 2016;23:353–4
78. Santoro N, Braunstein GD, Butts CL, Martin KA, McDermott M, Pinkerton JV. Compounded bioidentical hormones in endocrinology practice: an Endocrine Society scientific statement. *J Clin Endocrinol Metab* 2016;101:1318–43