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Body-identical Hormone Replacement Therapy: Micronised Progesterone is Finally Available in Australia

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This article discusses the novel body-identical progesterone compared to other hormone replacement therapies and its place in the treatment of menopause.

Introduction

Even though menopause is a normal physiological condition, for some women the consequences are devastating. Approximately half of all Australian women will have no or mild hot flushes when they become menopausal. However, around a quarter of women will have severe debilitating symptoms that cause fatigue, mood swings, difficulty concentrating at work and disrupted sleep. They may suffer loss of sexual desire that can contribute to relationship problems. Many of these women are not being treated for these problems, perhaps because they are not aware of the many options available, or because of fear of hormone replacement therapy (HRT).

This lack of effective management of menopausal symptoms was borne out in a recent publication by Professor Sue Davis' group in Melbourne.[1] They found that 29% of postmenopausal women under fifty-five years of age were having severe vasomotor symptoms, and these were also occurring in 15% of postmenopausal women aged fifty-five to fifty-nine years and 6.5% of women aged sixty to

Take Home Messages

- The lack of quality control and testing has led the International Menopause Society to instruct their members not to use handmade, compounded HRT in the form of troches, creams and pessaries.
- Oral (including troche) DHEA appears to have no role in the management of menopausal women and should not be included in a body-identical HRT regimen.
- Progestins negate much of the cardiovascular benefits of oestrogens and appear to be the HRT component linked to the slightly increased risk of breast cancer.
- Body-identical hormones are compounds that have exactly the same chemical and molecular structure as hormones that are produced in the human body.
- Micronised progesterone is superior to progestins in terms of safety profile and side-effects and may reduce hot flushes when used alone; it may be combined with systemic oestrogen.

sixty-nine years of age. The use of hormone replacement therapy (HRT), vaginal oestrogens and non-hormonal therapies for flushing (e.g. selective serotonin reuptake inhibitors) were 'strikingly low, suggesting that menopause remains an undertreated condition.' Many couples are putting up with painful sex, or have given up on sex, despite the fact that topical oestrogens are effective, safe, cheap and have been available for decades.

There are long-term consequences of menopause too, especially for those whose menopause occurs early (under forty years of age). These younger menopausal women, if untreated, are at increased risk of heart disease, osteoporosis, affective disorders and dementia.[2]

The public concerns fueled by the media about the safety of pharmaceutically produced hormones used at menopause has given rise to an entire industry based on bio-identical HRT. These are compounds that have exactly the same chemical and molecular structure as hormones that are produced in the human body, but are handmade, untested and compounded and used in the form of troches, creams and pessaries. However, the International Menopause Society warns against the use bio-identical HRT because of lack of standardisation in production. This may be associated with variation in concentrations of the hormonal components, potential contamination and incorrect dosage or administration of hormonal combinations leading to complications such as endometrial hyperplasia.

Recently, however, there has become a body-identical progestereone (micronised progesterone) that is superior to the synthetic progestins and bio-identical progesterones in terms of safety profile and side-effects. Micronised progesterone is pharmaceutically produced, medically standardised and of high quality, negating the concerns about bio-identical progesterones.

Don't All Hormone Replacement Therapies Increase Breast Cancer Risk?

Any practitioner who treats menopausal women knows that there is much fear around the use of HRT and that this is mostly linked to the risk of breast cancer. This fear started on the 10th of July 2002, when the Women's Health Initiative (WHI) Study released their preliminary results to the world media. It was stated that there was a 26% increased risk of breast cancer amongst those subjects who took conjugated oestrogens with medroxyprogesterone acetate (CEE-MPA).[3] In Australia, the headlines read 'Stop your HRT and see your doctor' (e.g. Daily Telegraph, 10th of July, 2002). This was widely interpreted by women as stating that HRT usage is linked to a one in four risk of breast cancer. It is well known amongst communication experts that unless a person is trained in statistics, percentages are

SOME COMMON DEFINITIONS*

Body-identical HRT: Compounds that have exactly the same chemical and molecular structure as hormones that are produced in the human body.

Bio-identical HRT: Compounds that have exactly the same chemical and molecular structure as hormones that are produced in the human body. In this article, these refer to human hormones that are handmade, untested and compounded in the form of troches, creams and pessaries.

Progestins: Synthetic compounds that have differing affinities for, and effects on the progesterone receptor; they may also activate non–progesterone receptor steroid receptors in different tissues.

Progesterone: This is the principal progestational steroid hormone, mostly produced by the corpus luteum to prepare the uterus for pregnancy. Large amounts of progesterone are also made by the placenta during pregnancy.

Micronised progesterone: An industrial process that produces a progesterone that has similarly sized, very small particles resulting in better absorption.

Progestogens: These include both progesterone and synthetic compounds that have progestogenic activity similar to that of progesterone.

Oestradiol (E2): 17βoestradiol is the predominant endogenous oestrogen circulating prior to menopause and is mainly secreted by the ovaries.

Oestrone: An endogenous oestrogen found in highest concentration after menopause and is converted in adipose tissue from oestradiol and adrenal androstenedione.

Oestriol (E3): The least potent and shortest acting endogenous oestrogen found in humans. Oestriol is formed through 16βhydroxylation of oestrone and oestradiol.

Files JA, Ko MG, Pruthi S. Bioidentical Hormone Therapy. Mayo Clin Proc. 2011 Jul; 86(7): 673-680. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3127562/

commonly misunderstood. In fact, the increased risk of breast cancer was only seen after five years of conjugated equine oestrogens (CEE) and medroxyprogesterone acetate (MPA) use and the absolute risk was eight per ten thousand women per year.[3] There were also eight other types of cancer prevented by the same HRT, (two fewer endometrial cancers and six fewer bowel cancers per ten thousand women per year), but this was not widely reported.[3]

There is now a widely held view that all HRT regimens are the same and that all of them increase breast cancer risk. Sadly, many women do not know that in the same study, those using CEE alone (hysterectomised patients) had a significantly decreased risk of breast cancer. Also, it is not well known that other HRTs, such as tibolone, are also associated with a decreased risk of breast cancer (LIFT study).[4]

'I Want to Use Natural Hormones'

Over the last few decades, women themselves have expressed an interest in using 'natural hormones.' Many are taking handmade, untested, compounded HRT in the form of troches, creams and pessaries. These products typically contain oestradiol (E2) and other oestrogens, progesterone, DHEA and often other human hormones. These are typically called 'bio-identical HRT' by their proponents. This topic has been reviewed by Cirgliano.[5] The lack of quality control and testing has led the International Menopause Society to instruct their members not to use such products.[6]

In Australia, we have had access to pharmaceutical grade E2 as tablets, patches, gels and vaginal products for decades. Oestriol (E3) is also available as tablets, pessaries and vaginal cream. Testosterone has been available as a cream (Lawley Pharmaceuticals; private script only). However, until recently, Australian women and their health practitioners have not had access to pharmaceutical-grade progesterone. As such, synthetic progestins have been used to protect the endometrium from the stimulatory effects of E2. They are very effective, but around one woman in eight develops side-effects similar to premenstrual tension, such as mood swings, feeling flat, depression and bloating. Also, progestins negate much of the cardiovascular benefits of oestrogens and appear to be the HRT component linked to the slightly increased risk of breast cancer.

The Europeans, especially the French, have published widely on the use of micronised progesterone (mP4) taken orally or vaginally, with E2 tablets, patches or gel. 'Micronisation' is an industrial process that produces a substance that has similarly sized, very small particles that result in better absorption. In brief, mP4 is superior to progestins in terms of safety profile and side-effects. For the first time in Australia, mP4 is now available as a pharmaceutical product. In the author's opinion, this will allow a 're-telling' of the HRT story and permit Australian women and their doctors to have access to tested, safe, effective and truly 'natural' HRT.

We have seen this evolution from biologicals/synthetics to the body-identical hormones in other areas of medicine too. Decades ago, insulin was extracted from the pancreases of animals such as cows or pigs. It worked, but there were problems, such as allergic reactions and tolerance. Once human insulins became available, we moved on from using the animal-derived products. The growth hormone and follicle stimulating hormone were also originally extracted from biological sources; now the human hormones are used and they are much safer.

In brief, micronised progesterone is superior to progestins in terms of safety profile and side-effects.

Guidelines for the usage of HRT have changed over the years and recently the International Menopause Society has published an excellent document reviewing the evidence base for the treatment of menopause.[6] The following is a link to this article, however registration and payment is first required: http://dx.doi.org/10.3109/13697137.2015.1129166 .

Body-identical Hormone Replacement Therapy

Dr Nick Panay points out that the term 'bio-identical hormones' is rather imprecise and is really a marketing term.[7] Bio-identical hormones are exact duplicates of the human hormones (such as E2, progesterone and testosterone). As previously mentioned, the term, 'bio-identical hormones,' is almost exclusively used by the compounding industry, which at the moment escapes the intense quality control, safety and efficacy testing demanded by the regulatory bodies for pharmaceuticals. In his paper, Dr Panay makes several points worth quoting directly:

'Compounding pharmacies market their own unregulated bio-identical products promoted in a number of countries by high-profile celebrities. Some practitioners prescribing these compounded preparations claim to be able to calculate the precise level of each deficiency from salivary hormones and then replace the precise amount using estrogen, progesterone and testosterone delivered

Body-identical HRT versus Bio-identical HRT

	Body-identical HRT	Bio-identical HRT
Quality of product	Pharmaceutical grade (highest quality)	Compounded (unknown quality)
Safety	Known, tested in controlled trial	Unknown
Efficacy	Superior to placebo	Unknown
Identical to human hormones	Yes	Likely

by lozenges or creams. This practice is not supported by evidenced for efficacy nor safety.'

Thus, body-identical HRT might be seen as pharmaceutical-grade, 'bio-identical HRT.' However, Dr Panay points out that 'bios' in Greek means 'life', and so he has coined the term 'body-identical HRT,' as a more accurate term to cover the prescribing of pharmaceutical grade human hormones such as progesterone and E2.

Body-identical sex hormones are typically derived from plant sources, such as soya or wild yam. Chemicals such as diosogen are extracted then converted in a laboratory into the various hormones. What is produced is identical to the human hormone.

Dr Panay goes on to make an interesting comment about the WHI Study and the differences between synthetic HRT and body-identical HRT:

'The adverse outcomes seen in the Women's Health Initiative (WHI) were mainly due to an over-dosage of hormones in a relatively elderly population. However, fundamental differences exist between conjugated equine estrogens and 17-beta estradiol and between medroxyprogesterone acetate and natural progesterone. It is likely that these differences also contributed to the adverse outcomes in WHI, which were contrary to the cardiovascular benefits seen in previous observational studies.'[7]

For the rest of this article, the term 'body-identical HRT' will be used. I will briefly discuss E2, DHEA and testosterone, but my main focus will be on the new product, mP4, 100mg and 200mg.

Oestradiol

Oestradiol was originally discovered in 1935 and is now available as tablets, patches, gel and a vaginal tablet. For most healthy women under sixty years of age, oral E2 is safe. However, oral E2 does undergo first-pass liver metabolism. This can be a positive effect (such as lowering total and low density lipoprotein cholesterol levels) or a negative effect (such as activating hepatic proteins such as the clotting factors, sex-hormone binding globulin [SHBG]).[7,8]

Thrombosis risk (deep venous thrombosis, pulmonary embolism and stroke) increases steadily with age and all the oral HRTs are associated with increased risk of thrombosis in older women (over sixty to sixty-five years of age).[3,4,8] Those with risk factors such as obesity, thrombophilia or past history of thrombosis should avoid oral oestradiol. In contrast, transdermal oestradiol (patches and gels) appears to have minimal or no increased risk of thrombosis.[8]

Vaginal E2 should not be inserted deep into the vagina, but rather delivered to the anterior vaginal wall. From a pharmacokinetic perspective, the vagina has two compartments. The posterior component has vascular and lymphatic connections with the uterus and so E2 placed in the posterior vagina, if used for long periods of time, could theoretically induce endometrial hyperplasia. The anterior compartment has connections with the urethra, clitoris and bladder[9] and so placement of E2 in this region best reduces atrophic symptoms.

Testosterone

The topic of testosterone replacement for women may be reviewed in detail elsewhere.[10-12] In summary, a woman with fatigue and loss of sex drive and who has a low total or free testosterone (the lower half of the normal range) may be considered for testosterone replacement.[10-12] Clearly, other causes of her presentation need to be excluded (such as iron deficiency, thyroid disease, hormonal contraception and relationship issues). The only pharmaceutical-grade testosterone product available in Australia is AndroFeme® 1% (Lawley Pharmaceuticals). The usual dose is 0.5-1.0mL of cream rubbed into the thigh daily, aiming to achieve a free androgen index (FAI) between 4-7%. Approximately two-thirds of women will find that energy levels and sexual desire will improve over three to six months.[12]

If E2 is given concomitantly with testosterone, then the transdermal route is preferable as oral E2 may increase SHBG levels (SHBG is a liver protein). High SHBG levels will result in a very low FAI and low free testosterone levels. Used appropriately, to date, no significant safety issues have been found with long-term use of testosterone replacement in women.[10-12]

WHY BODY-IDENTICAL HRT IS IMPORTANT

- Many patients want to use natural hormones rather than synthetic preparations
- Body-identical HRT has fewer side-effects than many synthetic hormone regimens
- Micronised progesterone used orally or vaginally has few side-effects compared to progestins
- HRT regimens containing mP4 appear to have a lower risk of breast cancer than those using synthetic preparations
- Micronised progesterone does not negate the cardiovascular benefits of oestrogen, unlike most progestins.The use of morphine in patients with renal impairment

Dehydroepiandrosterone

Dehydroepiandrosterone (DHEA) has been promoted (especially on the Internet) as an 'anti-ageing' hormone. It is the most abundant steroid in blood and levels fall with age. However, there is no receptor for DHEA in the human body. It can be inter-converted into oestrogens and androgens in tissues with the suitable enzyme systems (e.g. the vagina). There have been a number of randomised trials of DHEA and these have been reviewed.[13] In summary, there appears to be no therapeutic effect through giving systemic DHEA to menopausal women. Topical low-dose DHEA (6.5mg daily) applied to the vaginal epithelium does result in oestrogenic effects, with no measurable circulatory levels of oestrogenic or androgenic steroids.[14]

Oral (including troche) DHEA appears to have no role in the management of menopausal women and should not be included in a body-identical HRT regimen.

Recommended dosage of mP4 for women using E2 orally or transdermally:[19]

Oral route

Cyclical: 200mg mP4 for twelve to fourteen days per month
Continuous: 100mg mP4 daily

Vaginal route

Alternate day: 100mg mP4
Sequential: 45-100mg for at least 10 days a month
Minimal dose: 100mg twice a week (more research needed; endometrial monitoring may be required)

Transdermal route

Not recommended

Progesterone

Micronised progesterone is available in Australia from the 1st of September 2016 as Prometrium® (100mg) and Utrogestan® (200mg) gelatin caps.

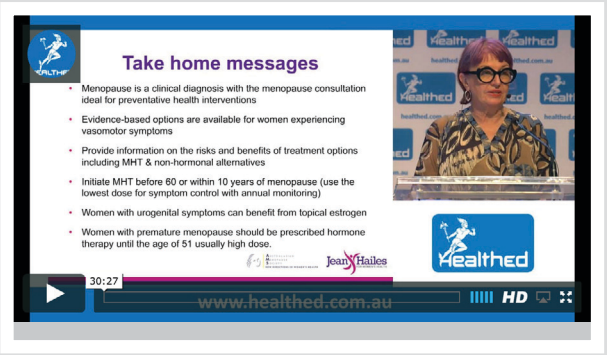
In broad terms, progesterone is a relatively difficult hormone to deliver to the human body (in contrast to oestrogens, which are readily absorbed via mouth, nose and skin). Micronisation of the particles greatly enhances absorption of progesterone. The PEPI Study[15] was a three-year study examining a number of safety endpoints for CEE (0.625mg), given with a variety of progestins. The Study demonstrated that the administration of oral mP4 (200mg) for twelve days per month effectively protected the endometrium against the stimulatory effects of CEE. Cuadros' group performed a ten-year study and showed that oral mP4 (100mg) taken daily with a 50ug E2 patch protected the endometrium and did not attenuate the cardiovascular benefits of the E2.[16]

Cicinelli[9] has reviewed the intravaginal delivery of E2 and mP4. The posterior vagina appears to be an excellent delivery site for mP4. In vitro fertilisation physicians have been using pessaries of mP4 to maintain pregnancies for years. Cincelli[17] performed a three-year study of thirty women who used E2 gel (Sandrena® gel) daily and mP4 100mg vaginally alternate daily. All developed endometrial atrophy on biopsy and amenorrhoea was achieved in 93% of cycles. Fernandez-Murga and colleagues[18] monitored sixty-four menopausal women, each using a 25ug/day E2 patch with vaginal mP4 100mg twice a week (inserted on the day of patch change). The number of subjects with amenorrhoea at twelve months was 100%. Endometrial thickness remained reduced and an atrophic endometrium was obtained in seven women who were biopsied. Pharmaceutical grade progesterone pessaries are also available in Australia. Stute and colleagues recently published a systematic review of the impact of mP4 on the endometrium. The results are summarised below.[19]

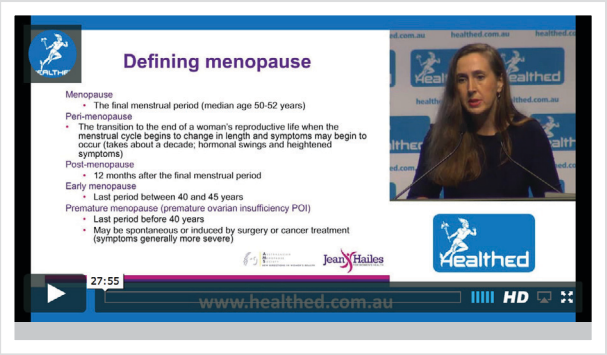
Cardiovascular Effects of mP4

Oestrogens can improve the cardiovascular risk profile (e.g. by improving the lipoprotein profile and through direct vascular effects). Typically, synthetic progestins antagonise these benefits.

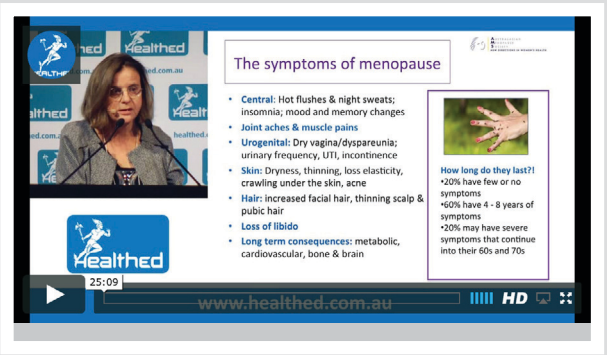
Video Resources



Menopause Management Update by Dr Elizabeth Farrell



Menopause Management Update by Dr Sonia Davison



Menopause Management Update by Bronwyn Stuckey

HRT and Breast Cancer by Prof Peter Ebeling

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Casanova has shown that mP4 does not alter the cardiovascular or metabolic effects of transdermal E2.[20]

Effects of mP4 on the Breast

The E3N-EPIC Study is a French prospective cohort study investigating cancer risk factors in nearly 100,000 women born between 1925 and 1950.[21] Since June 1990, subjects have filled in a two yearly questionnaire. The authors assessed breast cancer risk in 54,548 postmenopausal women who had never used HRT before entering into the study. There were 958 primary breast cancers detected over six years. The mean duration the subjects took HRT for was 2.8 years. The results are shown below. The breast cancer risk was higher for those exposed to synthetic progestins when compared to those using mP4 ($p<0.001$).[21]

Relative risk of breast cancer from the E3N-EPIC Study[21]

HRT used	RR (95%CI)
Oestrogen alone (mostly E2)	1. (0.8-1.6)
Oestrogen and progestin	1.4 (1.2-1.7)
Oestrogen and mP4	0.9 (0.7-1.2)

This observation was confirmed recently. Asi and colleagues published a meta-analysis comparing the breast cancer risk of women using oestrogen and mP4 with those using oestrogen and a synthetic progestin.[22] The included studies enrolled 86,881 postmenopausal women with mean age of fifty-nine years and follow-up of three to twenty years. Progesterone-oestrogen usage was associated with a significantly lower breast cancer risk compared with progestin-oestrogen users (RR 0.67; 96% CI 0.55-0.81).[22]

Campagnoli et al have reviewed the epidemiological and laboratory data on breast cancer risk with synthetic progestins versus mP4.[23] They concluded, 'The balance of the in vivo evidence is that progesterone does not have a cancer-promoting effects on breast tissue.' (p 104)[23]

Mood Effects of mP4

Progestins are responsible for most of the unwanted side-effects of HRT. Approximately 10% of women have side-effects similar to premenstrual tension when taking progestins such as MPA.[24] It is always worthwhile for the clinician to ask a menopausal patient how they felt on hormonal contraception. If they felt moody and irritable

on a levonorgesterol-containing contraceptive, then they are likely to dislike MPA or northisterone too. Micronised progesterone is much better tolerated in these circumstances.[24] Interestingly, a very small number of women become moody and irritable when taking oral mP4 as well. This is believed to be due to some reduced hepatic metabolites of P4. In these cases, evidence has shown the vaginal route, may be preferred, as there is no hepatic first-pass metabolism occurring (mP4 is not approved for vaginal administration in HRT in Australia).

The Use of mP4 Alone for Hot Flushes

While not an approved indication in Australia, it has been shown that 300mg of mP4 orally is superior to placebo for treatment of hot flushes.

Discussion

Many menopausal women having significant symptoms will prefer body-identical HRT. However, there is still a role for the other menopausal therapies. A Mirena® intrauterine device can effectively control the menstrual problems associated with the menopause transition. For some, a cyclical E2 therapy such as Trisequens®, Zoely® or Femoston® for one to two years will be appropriate and safe. Tibolone is a simple, effective and safe therapy for some menopausal women under the age of sixty years. Vaginal oestrogens are highly effective and safe (if placed in the anterior vaginal compartment) for vulvovaginal dryness[9] and they can help prevent urinary tract infections.

Fifty years of research has clearly shown that not all HRTs are the same. The WHI Study has shown that CEE-MPA used for more than five years is associated with a slightly increased risk of breast cancer (eight extra cases per ten thousand women per year).[3] However, in the WHI Study, oestrogen alone used for ten years did not increase breast cancer risk (and may even lower it). [3] Tibolone usage reduces breast cancer risk.[4]

However, many menopausal women having severe symptoms want to use body-identical HRT. Transdermal E2 (patch or gel) with micronised progesterone appears to be a safe and effective therapy for many of our patients. Most will take mP4 as a 100mg capsule daily (or 200mg cyclically), but for a very small number who can't take tablets or who have side-effects with oral mP4, then the topical vaginal route is available, although this would be off-label use in Australia.

Further reading

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Declaration

Dr John Eden was commissioned by Healthed for this article. The ideas, opinions and information presented are solely those of the author.

Dr John Eden declares no significant competing financial, professional or personal interests that might influence this article.

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A list of references is included in the website version of this article. Go to www.healthed.com.au/monographs

Summary

	Transdermal E2 with micronised progesterone	Oral CEE-MPA or oral E2 plus progestin
Effectiveness for treating menopausal symptoms	Effective	Effective
Impact on clotting system	Similar to placebo	Small increased risk of deep venous thrombosis, stroke (especially in older women)
Breast cancer risk	Similar to placebo; lower than progestin-regimens	After five years' usage, eight extra cases per 10,000 per year

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