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Effectiveness of transdermal oestradiol and natural micronised progesterone for menopausal symptoms

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INTRODUCTION

This article discusses the role of hormone replacement therapy (HRT) in the management of menopausal symptoms, and specifically considers the advantages of different types and preparations of HRT, based on the current medical evidence.

The menopause is a normal life event for women, not an illness or a medical condition. However, the effects of the menopause often have a negative impact on women's wellbeing and quality of life. Furthermore, the low oestrogen levels and other biological changes that occur in these women are also associated with an increased risk of cardiovascular disease, osteoporosis, diabetes, and dementia.

In addition to hot flushes and sweats, symptoms include mood changes, memory loss, urogenital atrophy, reduced libido, sleep disturbances, joint pains, and muscle stiffness.[1] These symptoms can be non-existent, or can last for a few years or even decades.

HRT 'SCARES' ARE UNFOUNDED

Much of the negative publicity surrounding HRT stems from misinterpretation by the media of the findings from the Women's Health Initiative (WHI) study,[2] published more than a decade ago. Many women and healthcare professionals are still unnecessarily concerned about the perceived risks of HRT, resulting in a significant proportion of women currently being refused HRT and often being inappropriately offered antidepressants.

EVIDENCE TO SUPPORT HRT

There is clear evidence to support that, in addition to a benefit on symptoms, HRT can also play a role in quality of life improvement, prevention of coronary heart disease, osteoporosis and fracture risk, and reduction in mortality. No other treatments for menopausal symptoms have demonstrated a similar role. This is reflected in current guideline recommendations including from the National Institute for Health and Care Excellence (NICE).[1,3,4]

Reassuringly, during a cumulative 18-year follow-up of WHI trials, women taking HRT did not have a higher risk of all-cause, cardiovascular, or cancer mortality.

TYPE OF HORMONE REPLACEMENT THERAPY

The benefits and risks of HRT vary by origin of product ('body identical', which are hormones that are chemically the same as those that the body produces, or equine), dosage, route of administration, and timing of initiation.[5]

HRT is available mainly as oral or transdermal preparations, all of which contain oestrogen, either alone or combined with progestogen.

MODE OF OESTROGEN DELIVERY

A systematic review and meta-analysis of treatment effects from NICE guidelines has shown that transdermal oestradiol had the highest probability of being the most effective treatment for vasomotor symptoms compared with placebo.[6]

Risk of venous thromboembolism

The overall venous thromboembolism (VTE) risk increases about two-fold in women who take oral oestrogens. High levels of oral oestrogen concentrate in the liver, which results in activation of the coagulation and activation factors of the renin–angiotensin–aldosterone cascade. In addition, oral (but not transdermal) oestrogens induce resistance to activated protein C. In contrast, studies have shown no association between VTE risk and use of transdermal oestrogens.

Guidelines recommend transdermal rather than oral HRT for menopausal women who are at increased risk of VTE, including those with a BMI >30 kg/m^2.[1]

Risk of stroke

Oral HRT containing oestrogen at either high or low doses is associated with an increased risk of ischaemic stroke, compared with non-

Box 1. The advantages of transdermal oestrogen and micronised progesterone

Transdermal oestrogen	Micronised progesterone
More reliable absorption than oral oestrogen	Oral preparation given with oestrogen as part of HRT, either cyclically or continuously
Less likely than oral oestrogen to cause side effects such as nausea	Neutral effect on blood pressure
Does not increase VTE risk even in women who are at high risk, such as those with prothrombotic mutations (including factor V Leiden)	Not associated with VTE risk unlike other progestogens
Should be first line in women with obesity, diabetes, or liver disease	Neutral effect on CVD risk unlike other progestogens
Oral oestrogen can lower libido by increasing SHBG levels whereas transdermal oestrogen does not have this effect	Less likely to cause side effects such as fluid retention
Does not have an increased stroke risk	Lower risk of breast cancer compared with progestogens
Costs around £4–£5 a month	Costs around £4 a month

CVD = cardiovascular disease. HRT = hormone replacement therapy. SHBG = sex hormone binding globulin VTE = venous thromboembolism.

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users. In contrast, transdermal preparations containing low doses of oestrogen have not been shown to be associated with this risk.

TYPE OF PROGESTOGEN

The progestogens used in HRT have distinctive biological and clinical profiles. They can be either a synthetic progesterone, which differs in structure from naturally occurring progesterone, or natural micronised progesterone (MP). This was developed in the 1980s and is produced from the yam plant. MP is chemically and structurally identical to human progesterone, and it is therefore often referred to as 'body identical' or 'natural'. The process of micronisation allows for a steady and even absorption. This can be prescribed either continuously or cyclically. The only current preparation available in the UK is Utrogestan® (Besins Healthcare (UK) Ltd).

Risk of venous thromboembolism

The risk of VTE is greater in women using medroxyprogesterone acetate compared with other progestogens. The risk of VTE increases by about 50% in women using oestrogen plus synthetic progestogens, compared with oral oestrogen alone. There does not appear to be this increased risk in women taking natural MP.

Cardiovascular risk

MP has been associated with a lower cardiovascular risk and has a neutral effect on blood pressure compared with synthetic progestogens, which have androgenic activities.

Risk of breast cancer

Women taking oestrogen-only HRT do not have an increased risk of breast cancer. It is only when a progestogen is added to the oestrogen-primed breast tissue that there is an increased risk. Progesterone and progestogens have different effects on the risk of breast cancer in menopausal women using HRT.[7]

A recent meta-analysis has shown that taking oestrogens combined with natural MP is not associated with an increased risk of breast cancer for the first 5 years. For women taking HRT for >5 years, risk of breast cancer was lower when taking MP compared with taking a synthetic progestogen.[8]

ENDOMETRIAL PROTECTION

Oral natural progesterone, taken cyclically and continuously, provides endometrial protection comparable with that given by other progestogens.

TOLERANCE

Side effects are less common with transdermal preparations of oestrogen, and current recommendations are to change the mode of administration (from oral to transdermal) if side effects occur.[1]

SUMMARY

It is very important that broad, sweeping conclusions concerning HRT are not made. It is essential that healthcare professionals, women, and also the media are aware that there are important differences between various HRT products.

There is robust evidence demonstrating that transdermal oestrogen in association with natural MP could represent the optimal HRT regimen, particularly in women at risk of cardiovascular events (Box 1).[5] This combination should ideally be initiated by healthcare professionals at a primary care level. The costs of these products are comparable with other types and formulations of HRT.

Provenance

Freely submitted; externally peer reviewed.

Competing interests

Louise Newson has had financial relationships (lecturer, writer, member of advisory boards, attendance at meetings, and/or consultant) with Pfizer, Meda, Mylan, Besins, Replens, Regelle, Sylk, MonaLisa Touch, and La Roche-Posay. These companies have had no control of the content of any lectures, articles, or other work she has done for them. Amir Lass has been previously contracted to a company manufacturing HRT products.