PRIMARY CARE
WOMEN'S HEALTH FORUM

Menopause – Guidance on management and prescribing HRT for GPs:

Based on NICE guidance 2015 and recent updates

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This document is in the process of being updated and does not currently reflect the 2024 update to the NICE guidance

INCLUDED IN THIS GUIDANCE:

1. A summary of the 2015 NICE guidance and other relevant studies
2. Oestrogens and progestogens used in HRT
3. A flow chart to use as a guide in choosing the appropriate treatment
   - Remember that all women are different, and this is a guide only; treatment must be individualised. There is a considerable variation in the individual's response to different types and routes of oestrogen for symptom control.
4. Possible medications to use - these are the drugs frequently used by the author; alternatives are available.

This resource was supported by an unrestricted educational grant from Viatris. Viatris has no editorial control over the content.
Date of creation September 2020.

1. SUMMARY 2015 NICE GUIDANCE: MANAGEMENT OF THE MENOPAUSE

Diagnosis

Diagnosis can be made without laboratory tests in otherwise healthy women aged over

45 years with appropriate symptoms:

- Perimenopause based on vasomotor symptoms and irregular periods.
- Menopause in women who have:
  - Not had a period for at least 12 months and are not using hormonal contraception. Or,
  - Symptoms in women without a uterus.

Consider using an FSH test to diagnose menopause only:

- in women aged 40 to 45 years with possible menopausal symptoms, including a change in their menstrual cycle.
- in women aged under 40 years in whom menopause is suspected.
- if possible, test day 2-5 of the cycle.
- FSH can be measured in women taking low dose progestogen-only contraception but not combined or depo-medroxyprogesterone. If not raised no inference can be drawn. If raised AND over the age of 50 the FSRH advise that the method can be discontinued after a further year. .
- Some women may have normal levels of FSH during the menopausal transition, so this should not exclude the perimenopause as a cause of their symptoms.

Vasomotor symptoms

- Offer women HRT after discussing with them the short-term (up to 5 years) and longer-term benefits and risks. Offer a choice of preparations as follows:
- Oestrogen and progestogen to women with a uterus
- Oestrogen alone to women without a uterus.

Do not offer selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs) or clonidine as first-line treatment for vasomotor symptoms.

Consider testosterone supplementation for menopausal women with low sexual desire if HRT alone is not sufficient.

Genitourinary syndrome of menopause

Vaginal oestrogen can be given to women with urogenital atrophy (including those on systemic HRT) and continued for as long as needed to relieve symptoms. Treatment should be started early before irreversible changes have occurred.

- If vaginal oestrogen does not relieve symptoms of urogenital atrophy, consider increasing the dose beyond the licensed twice-weekly dose after seeking advice from a healthcare professional with expertise in menopause. Vaginal moisturisers and lubricants can be used alone or in addition to vaginal oestrogen.
- There is no need for monitoring of endometrial thickness during the treatment of urogenital atrophy with vaginal oestrogens. However, advise women they should report unscheduled vaginal bleeding promptly.

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Venous thromboembolism

The risk of venous thromboembolism (VTE) is increased by oral HRT compared with baseline population risk (RR =2).

- The risk of VTE associated with HRT is more significant for oral than transdermal preparations.
- The risk associated with transdermal HRT given at standard therapeutic doses (<50mcg) is no greater than the baseline population risk.
  - Consider transdermal rather than oral HRT for menopausal women who are at increased risk of VTE, including those with a BMI over 30 kg/m^2.
  - Consider referring menopausal women at high risk of VTE (for example, those with a strong family history of VTE or a hereditary thrombophilia) to a haematologist for assessment before considering HRT.

Cardiovascular disease

- **HRT does not increase coronary heart disease risk when started in women aged under 60 years and does not affect the risk of dying from cardiovascular disease.**
- The presence of cardiovascular risk factors is not a contraindication to HRT as long as they are optimally managed.
- The baseline risk of coronary heart disease and stroke for women around menopausal age varies according to their personal cardiovascular risk factors.
- HRT with oestrogen alone is associated with no, or reduced, risk of coronary heart disease.
- HRT with oestrogen and progestogen is associated with little or no increase in the risk of coronary heart disease.
- Taking oral oestrogen (but not transdermal under 50mcg/24hr) is associated with a small increase in the risk of stroke, but the baseline population risk of stroke in women aged under 60 years is very low, so the increased risk is non-significant.

The all-cause mortality in women aged 50–59 years taking HRT on the two Woman's Health Institute (WHI[1]) randomised trials during the intervention phase was significantly reduced, and this reduction in mortality was still present at an 18-year follow up.

Type 2 diabetes

Taking HRT (either orally or transdermally) is not associated with an increased risk of developing type 2 diabetes.

In women with diabetes, HRT is not associated with an adverse effect on blood glucose control.

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Osteoporosis

Give women advice on bone health and discuss any risk factors for osteoporosis.

- The baseline population risk of fragility fracture for women around menopausal age in the UK is low and varies according to their personal and familial risk factors.
- Risk of fragility fracture is decreased while taking HRT but increases once treatment stops, although benefits may persist for a while in women who take HRT for longer.

HRT is the only treatment that gives protection against all fractures, even in women with normal bone density.

Women who have undergone an early menopause, either natural or surgical, should be prescribed HRT and advised to continue until at least the normal age of the menopause. Women with established osteoporosis aged under 60y, especially with menopausal symptoms, should be given HRT to improve their bone density.

Loss of muscle mass and strength

There is limited evidence suggesting that HRT may maintain muscle mass and strength, which otherwise tends to decrease after the menopause. Muscle mass and strength is also maintained through daily activities and weight-bearing exercise.

Breast cancer

The baseline risk of breast cancer for women around menopausal age varies according to the presence of underlying familial and environmental risk factors.

There is still no evidence of any increase in mortality from breast cancer in women taking HRT.

NICE stated that:

- HRT with oestrogen alone is associated with little or no increase in the risk of breast cancer.
- HRT with oestrogen and progestogen can be associated with an increase in the risk of breast cancer; however, any increase in the risk of breast cancer is related to treatment duration and reduces after stopping HRT.

NICE guidance was based on a review of studies meeting the GRADE criteria, including the largest RCT the Woman's Health Institute (WHI) study.

- This study suggested that if 1000 women used HRT for 5 years, there would be 4 extra cases of breast cancer with combined HRT use, and 4 fewer cases with oestrogen-only use, on a baseline risk of 15 cases per 1000 women over 5 years.
- Women who had not used HRT prior to the study showed no increase in breast cancer with combined HRT for 5 years, but a higher risk than never users with over 5 years of treatment.

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A meta-analysis of all available epidemiologic evidence on the association between HRT use and breast cancer risk was published in *The Lancet* in August 2019.

The meta-analysis concluded:

- Similar to the WHI, combined HRT regimens were associated with excess breast cancer risk. An excess risk was also seen with oestrogen-only regimens, unlike the reduction in risk seen in the WHI.
- Breast cancer risk increased after a year of use of all forms of systemic HRT and continued to increase with duration of use after that.
- The authors of the study calculated that for women of average weight, 5 years of HRT use starting at age 50 years would increase their 20-year risk of breast cancer (between the ages of 50 and 69 years) by approximately:
- 1 in every 50 users of oestrogen plus daily progestogen.
- 1 in every 70 users of oestrogen plus intermittent progestogen.
- 1 in every 200 users of oestrogen-only regimens.

There were significant limitations in this meta-analysis[2]:

- It included only observational studies, mainly composed of the Million Women Study. This study has been criticised for methodological flaws.
- The majority of women included in the analysis were using conjugated oestrogens and medroxyprogesterone acetate, not comparable with current HRT regimens using lower doses, different types and routes of administration of oestrogen, with micronised progesterone. This is now considered the progestogen of choice by most experts, as it is thought that transdermal 17-beta-estradiol and micronised progesterone may be associated with lower breast cancer risk than conjugated oestrogens and medroxyprogesterone acetate.

This meta-analysis has revived concerns amongst healthcare professionals regarding the association between HRT and breast cancer. In response the BMS, IMS, and RCOG issued a joint statement:

'*The meta-analysis provides important additional information on the risks of breast cancer, but it needs to be considered in the context of the benefits of HRT in treating vasomotor symptoms, improving sleep and quality of life for symptomatic women, and the prevention of bone loss.*

The findings from the meta-analysis are in keeping with the NICE guidance observational data on breast cancer risk, and ***discussions should also include findings from the WHI randomised trials and E3N observational studies which found no increased risk of breast cancer over five years with the use of oestradiol and micronised progesterone***.

An 18-year long-term follow-up study of the WHI randomised trials published in JAMA in 2020 concluded that use of CEE alone was significantly associated with lower breast cancer incidence and mortality, whereas the use of CEE plus MPA was associated with a higher breast cancer incidence, but no significant difference in breast cancer mortality.'

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Ovarian cancer

A 2015 meta-analysis of 52 epidemiological studies has shown an increased risk of ovarian cancer with oestrogen-only and combined HRT. Whilst this study provides evidence of an association between HRT use and some tumour subtypes, it provides insufficient evidence to claim that HRT causes ovarian cancer.

When counselling patients, it is essential to discuss these findings in terms of absolute risk.

With 5 years of HRT use, there could be 1 additional ovarian cancer per 1000 users and 1 additional death per 1700 users among women of all ages.

Premature ovarian insufficiency

In women with premature ovarian insufficiency (menopause under 40 years), it is essential to start hormonal treatment either with HRT or a combined hormonal contraceptive.

This treatment should be continued until at least the age of natural menopause (unless contraindicated) to protect against the increased risk of dementia, cognitive decline, cardiovascular disease and osteoporosis seen in these women.

- HRT has a negligible effect on blood pressure and beneficial effects on metabolic parameters when compared with a combined oral contraceptive.
- Both HRT and combined oral contraceptives offer bone protection.
- HRT is not a contraceptive.

Consider referring women with premature ovarian insufficiency to healthcare professionals who have the relevant experience to help them manage all aspects of physical and psychosocial health related to their condition.

REVIEW EACH TREATMENT FOR MENOPAUSAL SYMPTOMS:

- At 3 months to assess efficacy and tolerability
- Annually thereafter unless there are clinical indications for an earlier review (such as treatment ineffectiveness, side effects or adverse events).

2.OESTROGENS AND PROGESTOGENS

All routes of oestrogen administration are equally effective for symptom relief and bone protection, but their metabolic effects differ.

- Oral oestrogen increases sex hormone binding globulin (SHBG) levels which can result in lower free testosterone concentrations, a benefit if women are noticing postmenopausal hirsutism.
- Transdermal preparations can be started at a low dose such as Estradiol 25 µg patch, or one measure of Estradiol gel and titrated up until symptoms are alleviated. If symptoms are still present after 1 month, an increase to 37.5 µg, then 50 µg (patch or gel) is associated with fewer side effects such as breast tenderness and vaginal bleeding, and also keeps risks minimised.
- The increased VTE risk seen with oral preparations is not found using transdermal preparations under 50mcg estradiol gel.
- Most women find a standard dose of a 50µg patch or two measures of estradiol gel are adequate for symptom relief; the only exception is younger women either after oophorectomy or with premature ovarian insufficiency who often require higher doses of estradiol.
- In women who are still experiencing some periods, a cyclical progestogen regime is required in order to regulate the cycles, encouraging a bleed around the end of each month. Cyclical oral formulations contain older progestogens which protect the endometrium but may have progestogenic side effects.
- For perimenopausal women, micronised progesterone 200 mg a day can be used for 14 days of each month. In women who are more than a year post-last period or have used a cyclical preparation for 2 to 3 years this can be transferred to a continuous regime using micronised progesterone 100 mg daily, which should keep women amenorrhoeic.
- Micronised progesterone or dydrogesterone should be the first choices of progestogen as they appear to be safer for the cardiovascular system, having neutral effect on lipids and coagulation, and a lower risk of breast cancer.

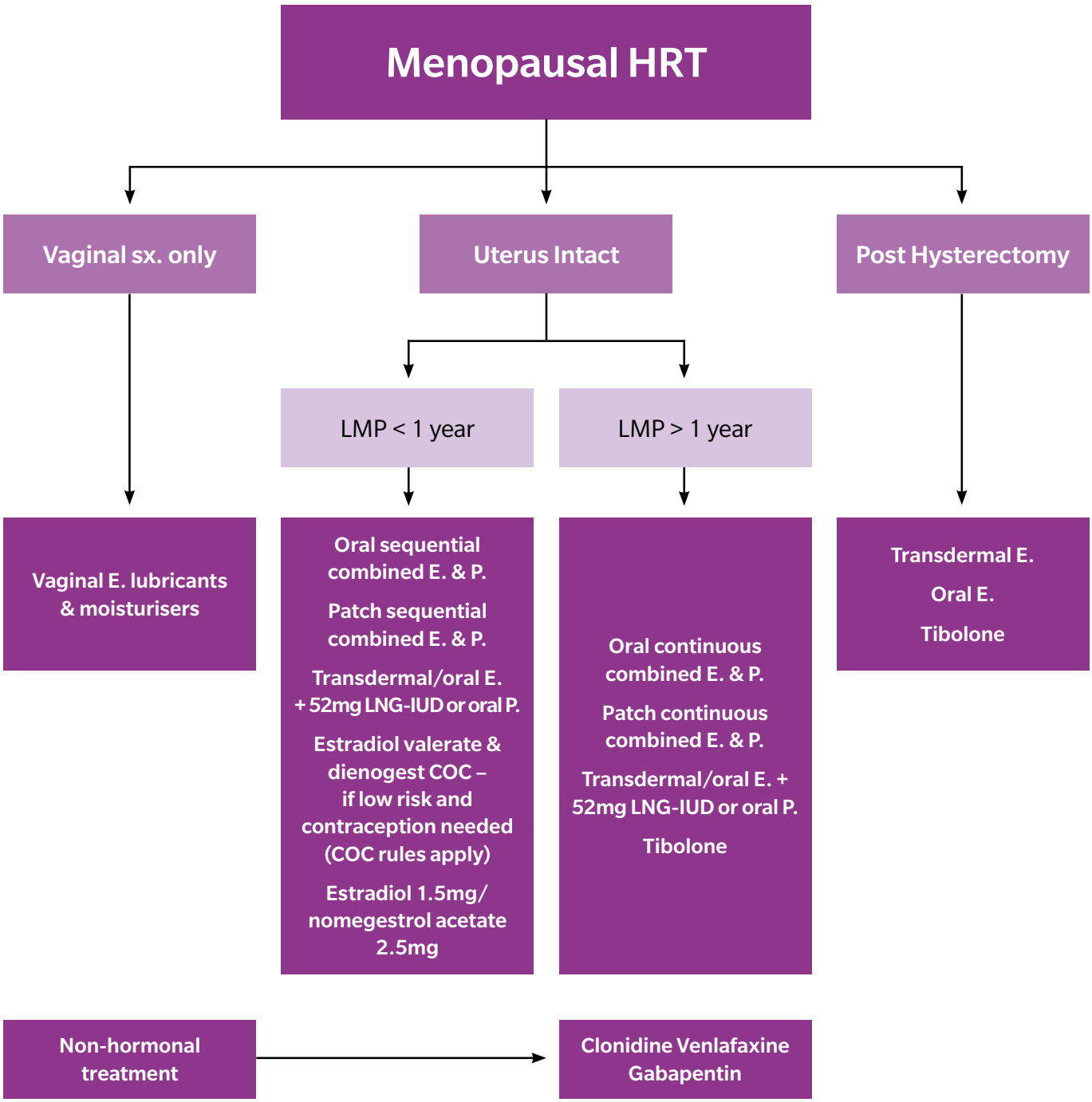
2.OESTROGENS AND PROGESTOGENS

TYPE OF PROGESTOGEN	GOOD FOR	WATCH OUT FOR	PRESCRIBED AS
SYNTHETIC: C19 TESTOSTERONE DERIVATIVES			
Norethisterone	Cycle control Androgenic – good for libido	Some degree of estrogenic effect caution if VTE risk ++	E2/Net fixed combined tablet/patch or as stand alone
Levonorgestrel As IUD	Cycle control Low systemic absorption Excellent contraception Good for HMB	Androgenic effects (acne, mood) PMS	52mg LNG-IUD Or In combined patch
SYNTHETIC: C21 PROGESTERONE DERIVATIVES			
Medroxyprogesterone acetate	Cycle control	Caution if VTE risk +	SCHRT – E2 plus 10–20mg cyclically CCHRT- E2 plus 5mg conti Or fixed dose in oral
Dydrogesterone	Non-androgenic so good if PMS type side effects	Only available with oral oestrogen	Oral fixed dose Sequential (including low dose) or combined
Natural progesterone: Micronised progesterone	Fewer progestogenic side effects No androgenic or glucocorticoid activity No impact on lipids Oral product can be used vaginally at same dose (though unlicensed) to reduce mood or gut side effects.	Less effective cycle control Take at night as may cause sedation	Sequential – 200mg cyclically Or Continuous 100mg daily

Table 1: Progestogens currently licenced for use in the UK as part of combined HRT[3]

PROGESTOGEN	OESTROGENIC	ANTI-OESTRO-GENIC	ANDROGENIC	ANTI-ANDRO-GENIC	GLUCOCORTI-COID	ANTIMINERALO-CORTICOID
Norethisterone	✓	✓	✓	×	×	×
Levonorgestrel/ Norgestrel (including intrauterine devices)	×	✓	✓	×	×	×
Progesterone	×	✓	×	✓	✓	✓
Medroxyprogesterone acetate	×	✓	✓	×	✓	×
Dydrogesterone	×	✓	×	✓	×	✓

3. FLOWCHART FOR HRT PRESCRIBING



4. POSSIBLE MEDICATIONS TO USE – there are alternatives available, see the BNF

HRT	TABLETS*	2ND LINE*	TRANSDERMAL*
SEQUENTIAL PREPARATIONS For patients with: • intact uterus • perimenopausal-under 1yr or amenorrhoea	**Estradiol 1mg + Norethisterone sequential** **Estradiol 2mg + Norethisterone sequential**	**Estradiol + Dydrogesterone 1/10mg sequential** **Estradiol + Dydrogesterone 2/10mg sequential** (Non-androgenic)	**Estradiol 50mcg + Levonorgestrel 10mcg SEQUI patch** **Estradiol 50mcg + Norethisterone 170mcg SEQUI patch**
CONTINUOUS COMBINED Bleed free HRT use if: • Over 1yr since last period • >54y • >3yrs on sequential HRT	**Estradiol 2mg + Norethisterone 1mg CONTI** **Estradiol 0.5mg + Dydrogesterone 2.5mg CONTI** **Estradiol 1mg + Dydrogesterone 5mg CONTI**	**TIBOLONE 2.5mg** Can be useful if: • Bloating on oestrogen • Poor libido • Endometriosis	**Estradiol 50mcg + Levonorgestrel 7mcg CONTI patch** **Estradiol 50mcg + Norethisterone 170mcg CONTI patch**
UNOPPOSED OESTROGEN Post hysterectomy	**Estradiol 1mg tablets** **Estradiol 2mg tablets**		**ESTRADIOL PATCH** 25mcg, 37.5mcg, 50mcg, 75mcg, 100mcg **Estradiol 0.06% gel** **Estradiol 500mcg or 1mg gel sachets**
TOPICAL VAGINAL OESTROGEN			**Estradiol 10mcg** vaginal pessaries **Estriol 0.1% CREAM** Estradiol vaginal ring
PROGESTOGEN ADJUNCT TO TOPICAL OESTROGEN IF NO HYSTERECTOMY	**Medroxyprogesterone** 10mg d14-28 or 2.5-5mg daily˚ **Micronised progesterone** Oral product can be used vaginally at same dose (though unlicensed) to reduce mood or gut side effects	**Levonorgestrel intrauterine system 52mg** Replace after five years as per FSRH guidance	

*Use the lowest dose to control symptoms. ˚Day 14-28 (sequential – i.e. still giving periods), daily for continuous combined (bleed-free)

Testosterone use

Please refer to the PCWHF resource: XXXXXXXXXXXXXXXXXXXXXXXX

https://www.pcwhs.co.uk/resources/7/10_top_tips_on_testosterone_use_for_women/

REFERENCES **1** https://www.nhlbi.nih.gov/science/womens-health-initiative-whi **2** J. C. Stevenson & R. D. T. Farmer (2020) HRT and breast cancer: a million women ride again, Climacteric, 23:3, 226-228, DOI: 10.1080/13697137.2020.1735797 **3** Original information courtesy of Mylan (n.d.). The importance of the progestogenic component of hormone replacement therapy in women with a uterus. [online] Guidelines. Available at: https://www.guidelines.co.uk/supplements/the-importance-of-the-progestogenic-component-of-hormone-replacement-therapy-in-women-with-a-uterus/454874.article [Accessed 19 Sep. 2020].