HRT Guidance and Treatment Pathway

NHS Wiltshire Clinical Commissioning Group

ORAL TREATMENT OPTIONS

Oestrogen Only
(no uterus)
1 prescription charge

- **Elleste Solo** 1mg or 2mg estradiol
- **Premarin** 0.625mg or 1.25mg conjugated oestrogen

Sequential combined
(uterus - monthly bleed)
2 prescripton charges

- **Elleste Duet** 1mg or 2mg estradiol + 1mg norethisterone
- **Prempak-C** 0.625mg or 1.25mg conjugated oestrogen + norgestrel 150mcg
- **Progestogenic side effects** (see text for further information)
  Femoston 1/10 or 2/10 1mg or 2mg estradiol + dydrogesterone 10mg

Continuous combined
Women should have had NO periods for 2 yrs if <50yrs old, 1 year if >50 yrs old or be 54
(uterus - no bleed)
1 prescription charge

- **Elleste Duet Conti** 2mg estradiol +1mg norethisterone
- **Premique** conjugated oestrogen 625mcg + medroxyprogesterone acetate 5mg
- **Kliofem** 2mg estradiol + 1mg norethisterone
- **Tibolone (Livial)** (See text for full guidance)
- **Progestogenic side effects:**
  Femoston Conti ‡
  1mg estradiol + 5mg dydrogesterone

Older women (60yrs plus) / low dose preparations

- For this group of patients, they may require less oestrogen as found in the following products:
- Oestrogen only
  - Premarin 300mcg (conjugated oestrogen)
  - Evorel 25 patch 25mcg/24hrs
  - Oestrogel (estradiol 0.75mg/measure, 1 measure= low dose)
- Continuous combined :
  - Premique low dose 300mcg (conjugated oestrogen and medroxyprogesterone acetate 1.5mg)
  - Kliovance (estradiol 1mg and norethisterone acetate 500mcg)

Atrophic vaginitis

Ovestin (0.1% estriol vaginal cream)
or Vagifem (10mcg vaginal tablet)
To initiate (reducing course):

- Use once a night for 14 nights
- Then alternate nights for 14 nights †
- Twice per week thereafter
- Continue while therapeutic benefit

TRANSDERMAL TREATMENT OPTIONS (if oral route C/I / not tolerated / unsuitable

Oestrogen only

- **Evorel** patches Change TWICE per week 25, 50, 75, 100mcg estradiol
- **Estradot** patches Change TWICE per week 25, 37.5, 50, 75, 100mcg estradiol
- **Oestrogel** 0.06% oestradiol gel, 0.75mg estradiol per measure, 2 measures= standard regime

Sequential combined HRT

- **Evorel Sequi** patches Change TWICE per week 50mcg estradiol + 170mcg norethisterone
- **FemSeven Sequi** patches Change ONCE weekly 50mcg estradiol + 10mcg levonorgestrel

Continuous combined HRT

- **Evorel-Conti** patches Change TWICE per week 50mcg estradiol + 170mcg norethisterone
- **If progestogenic side effects:**
  FemSeven Conti patches Change ONCE weekly 50mcg estradiol + 7mcg levonorgestrel

Refer patients for advice if no products are suitable

†This is an extra step which allows slower reduction than the license, as recommended by local specialists
‡ If patient has menopausal symptoms (e.g. hot flushes) on this preparation, the estradiol may need increasing to 2mg by adding in a 1mg elleste solo tablet.

Indications

- Relief of vasomotor symptoms (short-term) e.g. hot flushes and night sweats.
- Prevention/treatment of osteoporosis (long-term).
- Premature ovarian failure.
- Relief of other menopausal symptoms e.g. sleep disturbance, anxiety and depression, sexual function.

Contraindications

- Pregnancy.
- Undiagnosed abnormal vaginal bleeding.
- Active thromboembolic disorder or acute-phase myocardial infarction.
- Suspected or active breast or endometrial cancer.
- Active liver disease with abnormal liver function tests.
- Porphyria cutanea tarda.

Modifiable lifestyle factors - *ensure that these are addressed*

- Women should be advised to eat a healthy balanced diet, to maintain a healthy BMI, to ensure they eat sufficient dietary calcium (700mg/day) and undertake regular weight-bearing exercise.
- Ensure that a discussion occurs with the patient in order to address stopping smoking, reducing alcohol intake.
- Ensure optimum treatment of conditions such as diabetes and blood pressure as applicable in order to reduce the impact of such diseases on menopausal symptoms.

Management of menopause

- Women should only be prescribed HRT in the context of a supportive consultation with their healthcare provider.
- HRT should only be prescribed in the context of a full medical history, including personal, family and drug history and in the knowledge of basic parameters e.g. Height/weight, BMI, BP.
- Patients should be up to date with screening such as cervical cytology and mammography.
- Women who have >6/12 amenorrhea and then bleed should be considered for further investigation.
- There are non-hormonal alternatives for menopause treatment, but none are as effective as HRT. Further information can be found at: www.menopausematters/remedies.php
- **In all patients allow 3 months on treatment before making any changes as side-effects frequently subside with use.**

Premature menopause

- Increased risk of osteoporosis and ischaemic heart disease due to early loss of oestrogens.
- HRT should be taken at least until the age of normal menopause and probably for 5-10 years after the age of 50.
- In women who have had surgically-induced menopause, HRT is recommended until the age of 52 and for 5-10 years after this age if it is indicated to do so.
- In women who have had a hysterectomy with ovarian conservation, it is good clinical practice to do an annual FSH level.

Perimenopausal women

- Perimenopausal women may still need contraception. They should continue to use contraception for 1 year after the last period if they are over the age of 50, or for 2 years if under 50 years of age or arbitrarily if using the mini-pill or HRT until their 56th birthday.
- In those without contra-indications, combined hormonal contraceptive preparations will treat vasomotor symptoms and reduce fracture risk.
- For most women aged around 50 or above, using HRT for short-term (approximately 5 years) menopausal symptom relief will confer benefit and not harm.
- In terms of the choice of HRT preparation (i.e. cyclical or continuous combined), the age limits are similar as set out for contraception above. Also see treatment pathway (page 3).
- It is not recommended to initiate HRT in women over age 60 years solely for the purpose of prevention of ischaemic heart disease.

Oral - Usually first choice

- Cost-effective and acceptable for the majority of patients.

Patches - For patients with conditions including the following:

- Poor symptom control with oral treatment.
- History of, or risk of venous thrombo-embolism (refer such patients to a specialist in order to assess the risk and choose the most appropriate regimen).
- Variable hypertension (BP should be controlled before starting HRT).
- Hypertriglyceridaemia.
- Bowel disorder which may affect absorption of oral therapy.
- History of migraine (when steadier hormone levels may be beneficial).

Side-effects on oral preparations.
Current hepatic enzyme inducing agent e.g. anticonvulsants
Lactose Sensitivity.
History of gall stones.

Benefits of HRT:

- Reduction of vasomotor symptoms.
- Improved sleep, joint pain and quality of life.
- Relief of vaginal dryness and improved sexual function.
- Improved bone mineral density and reduced fracture risk.
- HRT may improve psychological symptoms e.g. depression and anxiety.
- Other possible benefits include the reduction in risk of colonic cancer, dementia/Alzheimers, prevention of diabetes, macular degeneration and cataract formation, with improved dentition and skin healing – these are still controversial and not seen as indications.

Risks of HRT:

- Much controversy exists about the risks of taking HRT. However, experts now agree that the key recent studies underlying these controversies, notably the Million Women Study (MWS) and the Womens Health Institue (WHI) had serious methodological flaws.
- The results of these studies should be viewed with caution. A helpful patient information leaflet can be found at: http://www.womens-health-concern.org/help/factsheets/fs_hrtrisksbenefits.html
- For further information on the risks of HRT see: http://www.thebms.org.uk/factdetail.php?id=6
- Brief estimates of the risks are as follows:

Breast Cancer	Women under the age of 50 on HRT are at no extra risk of breast cancer than they would be if their ovaries were working normally. There may be a small increase in breast cancer in women who use HRT long-term. This is mostly confined to women on combined HRT (not in women on oestrogen alone). There will be 3 extra cases of breast cancer per 1000 women who use combined HRT (aged 50-59) per 5 years of use.
Ovarian Cancer	Studies are conflicting. If there is a risk it is very small. If 2,500 women take HRT for 5 years, there would be 1 extra case of ovarian cancer.
Endometrial Cancer	Giving women HRT oestrogen alone, if they have a uterus, increases their risk of endometrial hyperplasia and cancer. The addition of progestogen greatly reduces this risk. Continuous combined HRT gives better endometrial protection than cyclical HRT. Women should be converted to a continuous combined ("no bleed") preparation within 5 years of starting HRT where possible.
Venous Thromboembolism	The background risk of VTE in middle-aged women is low. HRT may increase the risk 2-3 times, but the risk is still small.
Cardiovascular Disease	Final analysis of the WHI study showed no increased risk of ischaemic heart disease (IHD) in women on oestrogen-only HRT. In fact there was a reduced risk compared to placebo. IHD risk was only increased in women who started HRT over the age of 60. There may be a "window of opportunity" where HRT is started i.e. it confers benefit not harm.

Putting the risks into perspective

- Comparing other known risk factors for breast cancer with HRT risk can be helpful in putting risk into perspective:
  - more than 2-3 units of alcohol per day increases risk by 1.5x.
  - postmenopausal obesity by 1.6x.
  - late first pregnancy (more than age 30) by 1.9x.
  - more than 5 years of HRT by 1.35x.
- For more information visit www.menopausematters.co.uk/risks.php

Counselling Points

- Warn women of the bleed pattern with the chosen regimen. Irregular bleeding is common in the first 3-6 months of use.
- Reinforce the importance of adherence with therapy.
- Remind peri-menopausal women that HRT is not a contraceptive and that contraceptive precautions are still necessary.
- There is no evidence that HRT causes weight gain.

Poor Symptom Control

- Check compliance - allow 3 to 6 months on therapy to ensure full effect.
- Poor patch adhesion or skin irritation from patch -try alternative brand.
- Inadequate estrogen dosage – increase dose or change from oral to non-oral route.
- Incorrect diagnosis –review indications (e.g. thyroid disease) or refer.
- Poor absorption due to bowel disorder –change to non-oral route.
- Unrealistic expectations –counsel.
- Drug interactions : enzyme inducers lower the circulating levels of hormone e.g. barbiturates, phenytoin, carbamazepine – increase oral dose (both oestrogen and progestogen - i.e. double the dose) or change to non-oral route. Intra-Uterine Systems are not affected.

Side Effect Management Table

- Side effects can be categorised into Estrogenic and Progestogenic.
- There is no evidence that HRT causes weight gain.
- There are 2 groups of progestogens: testosterone derived and progesterone derived.
- Women who have troublesome side effects from a progesterone in the testosterone group, eg breast tenderness, mood swings, acne, may find these side effects improve if they try a progesterone from the progesterone group and vice versa:

Estrogenic			
Breast tenderness, enlargement Leg cramps Bloating Nausea Headache	For breast symptoms	Reduce dose of estrogen or change route. **OTC Purchase**: Evening Primrose oil, starflower oil.	
	For gastrointestinal symptoms	Take with food or change route.	
	Other side effects	Change type or route.	
Progestogenic			
PMS type symptoms Breast tenderness Lower abdominal pain Backache Depressed mood Acne/greasy skin Headache	Change to alternative progestogen	***Testosterone*** derived: Norethisterone, Norgestrel, Levonorgestrel.	***Progesterone*** derived: Medroxyprogesterone, Dydrogesterone, Drospirenone.
	Change route	Give progesterone by LNG-IUS (Mirena coil) to avoid side effects.	
	If postmenopausal, change to continuous combined HRT or tibolone	Avoids symptoms of progestogen fluctuation.	

Adapted from http://www.menopausematters.co.uk/sideeffects.php

Refer to a menopause specialist if changes made have no effect

When to refer

- Persistent side effects following logical therapy changes as per side effect management section
- Inadequate control/failure to respond despite logical changes in HRT as per poor symptom control
- Difficulty diagnosing menopause
- Loss of libido causing signifcant distress
- Difficult decisions regarding when to stop or start HRT
- Patient request
- Premature menopause
- Concerns over the safety of using HRT in a particular patient
- Complex medical history
- **Bleeding problems:**
  - During sequential therapy – change in pattern of bleeding including increased duration, frequency and/or heaviness, and irregular bleeding. Patients should have a bleed at the beginning of a new pack of tablets, when they are starting an oestrogen-only phase. If the patient is bleeding earlier than this, then it indicates that they need extra progestogen to be added into their regimen or seek advice from a menopause specialist for a suitable regimen, especially if bleeding pattern does not improve.
  - During continuous combined therapy or tibolone – if still bleeding after 6 months of therapy or if bleeding occurs after a spell of amenorrhoea refer.
  - Selective estrogen receptor modulators (SERMs) – any bleeding whilst on therapy should be treated as a post menopausal bleed and warrants investigation.
- History of hormone dependent cancer, and patients with BRACA genes.

Follow up guidance/ Initial follow up after initiation or a change in formulation

- See after 3 months to assess effect of therapy, enquire about side effects and bleeding pattern.

Annual review (when settled)

- Check effectiveness of therapy and presence of side effects, update on best type of therapy for patients, ensure the correct dose, optimal route of delivery, compliance and side effects.
- Discuss pros and cons of continuing HRT, in particular increased risk of breast cancer with long-term HRT - do benefits continue to outweigh risks?
- Check blood pressure, encourage breast awareness/ attendance of screening mammography.
- Assess osteoporosis risk and consider the need for investigation/monitoring.
- Ensure cervical screening is up to date.
- Enquire about symptoms of vaginal atrophy.

Duration of treatment

- Most guidelines recommend that the use of HRT for around 5 years in women as they enter menopause (ie in their late 40's/early 50's) is likely to confer benefit and not harm.
- There are no reasons to place mandatory limitations on the duration of HRT, which should be decided with a well informed woman and her health professional, dependent on her specific goals and objective estimate of risks and benefits.
- Withdraw HRT slowly as this may reduce the chance of recurrent sypmtoms. It should be noted that 5% of women will have hot flushes for life.

When to stop contraception

- The general rules are to continue contraception for:
  - One more year following the last spontaneous menstrual period if aged 50 years or over
  - Two more years following the last spontaneous menstrual period if aged under 50 years
- Fit, healthy, non-smoking women may continue the combined oral contraceptive (COC) pill up to the age of 50. There may be cardiovascular benefit for older women to use lower dose COCs (20mcg ethinyloestradiol). HRT may be used in women taking progestogen-only pills.

Levonorgestrel Intrauterine System (LNG-IUS) (Mirena® Coil)

- This is an intra-uterine hormone delivery system.
- Once inserted into the uterine cavity, the levonorgestrel component causes endometrial atrophy.
- The device also results in disturbance of ovulation and the development of hostile cervical mucous.
- It is licensed as a contraceptive, to treat menorrhagia and to give endometrial protection as part of HRT.
- Once the IUS is in place, if being used as part of an HRT regime, the woman only needs to take HRT oestrogen as a tablet, patch or topical gel.
- If this IUS is being used as part of a HRT regime, it only has a 4 year license.
- Irregular bleeing is common in the first few months of use. An IUS should only be inserted into a perimenopausal woman, after an appropriate gynaecological/menstrual history and after appropriate assessment/investigation. Once in-situ, periods may be reduced by >95% by 6 months, and approximately 20% of users will be completely amenorrheic.
- An IUS should only be inserted by an appropriately trained practitioner.

Additional treatment options

Testosterone

- Testosterone therapy may be an effective treatment for women experiencing loss of libido that is causing distress i.e. Hypoactive Sexual Desire Disorder (HSDD).
- The key group are women who have had a hysterectomy and bilateral salpingo-oopherectomy, who have lost 50% of their circulating testosterone. However, even women going through a natural menopause, uterus and ovaries intact, may in some circumstances, benefit from testosterone replacement.
- There are **no licensed treatments available for women**.
- There are many issues affecting libido, so if testosterone replacement is being considered, specialist referral is advised.

Tibolone (gonadomimetic)

- Tibolone is a synthetic steroid with oestrogenic, progestogenic and androgenic activity. As such, it is a type of continuous combined HRT and so is a no bleed preparation. Because of its androgenic activity, it has been shown to have a positive effect on libido.
- Tibolone has been shown to be as/or more effective than oestradiol in controlling menopausal symptoms.
- Although 85% of Tibolone users are amenorrhoeic, there is an 11% chance of irregular bleeding, so this may require gynaecological investigation.
- Prescribing of Tibolone should take into account the risks of other forms of HRT, such as a possible increase in breast cancer or
- Tibolone may enhance the effect of anticoagulants such as warfarin, so caution is advised in the concomitant use, especially when starting or stopping treatment.

References:

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Pt info leaflets: http://www.menopausematters.co.uk/oestrogens.php