DERBYSHIRE JOINT AREA PRESCRIBING COMMITTEE (JAPC)

MENOPAUSE MANAGEMENT GUIDELINE (based on NICE NG23)

- Diagnose menopause/ perimenopause without laboratory tests in otherwise healthy women aged over 45 years with menopausal symptoms.
- Give information in different formats on the cause of the menopause, common symptoms, long term health implications, health improving lifestyle changes and interventions, benefits and risks of hormonal, non-hormonal and non-pharmaceutical treatments.
- Offer Hormone Replacement Therapy (HRT) first-line for menopausal related vasomotor symptoms after discussing short term and long term benefits and risks.
- Review HRT treatment 3 months after commencing, and annually thereafter once settled on treatment. Do not set arbitrary limits for duration of use since length of symptoms cannot be predicted. Offer women who are stopping HRT a choice of gradually reducing (may limit recurrence of symptoms short term) or immediately stopping treatment, which makes no difference to symptoms in longer term.
- Selective serotonin uptake inhibitors (SSRI), selective noradrenaline uptake inhibitors (SNRI) antidepressants or clonidine should **not** be routinely offered first line treatment for vasomotor symptoms. For menopause related low mood, consider HRT and or cognitive behavioural therapy (CBT) (SSRIs and SNRIs have not been shown to help unless depression is diagnosed)
- Topical testosterone gel (Testogel) is Green after specialist recommendation for use in patients whose HRT does not improve low sexual desire on its own (unlicensed indication). Specialist will provide dose & instruction for its use.
- Offer and continue vaginal oestrogen to relieve symptoms of urogenital atrophy (usually long-term as symptoms recur on stopping vaginal oestrogen). Do not routinely measure endometrial thickness to monitor treatment. Women should be advised to report any unscheduled bleeding to their GP. (Higher dose may be indicated temporarily- contact a local menopause expert for advice)
- Women who are likely to start menopause because of medical or surgical treatment need support and information about it before treatment starts.

Ovarian insufficiency

- Diagnose premature ovarian insufficiency in women aged under 40 years based on: menopausal symptoms, including no or infrequent periods (taking into account whether the woman has a uterus) **and** elevated FSH levels on **two** blood samples taken 4–6 weeks apart.
- Explain the importance of starting either with HRT or a combined hormonal contraceptive and continuing treatment until at least the age of natural menopause (51 years) unless contraindicated.

Risks associated with HRT (see appendix 1)

- HRT **does not** increase cardiovascular (CVS) risk when started under age 60 – HRT is not contraindicated in women with optimally managed CVS risk factors (eg hypertension, diabetes).
- Consider transdermal HRT in women with a higher background VTE risk including those with a BMI over 30 kg/m^2 as oral HRT is associated with a higher risk of venous thromboembolism.
- HRT with oestrogen (ET) alone is associated with little or no change in the risk of breast cancer, combined oestrogen and progestogen HRT (CET) can be associated with an increase in the risk of breast cancer: however the latter is required in women with a uterus.

Background

The average age for the natural menopause in the UK is 51: premature menopause affects 1 in 100 women under the age of 40. About 80% women experience some symptoms (est 1.5 million women nationally). Symptoms often last for about 4 years but in about 10% of women can last for 12 years or more.

Menopause symptoms are often misunderstood, ridiculed and underestimated. However they may severely affect a woman's health and quality of life. Hot flushes and sweats can sometimes be so bad they constantly interrupt sleep and can leave sufferers drenched in sweat and exhausted. Menopause also can result in low mood, osteoporosis and urogenital changes that can cause vaginal dryness, urinary tract infections, and adversely affect a woman's sex life.

It is hoped that the guideline will not only support healthcare professionals but also provide women with the necessary information to empower them to go and talk to their healthcare professionals to help them make informed decisions about their choice of treatment.

Definitions

Perimenopause	The time in which a woman has irregular cycles of ovulation and menstruation leading up to menopause and continuing until 12 months after her final period. The perimenopause is also known as the menopausal transition or climacteric.
Postmenopause	The time after menopause has occurred, starting when a woman has not had a period for 12 consecutive months.
Premature ovarian insufficiency	Menopause occurring before the age of 40 years (also known as premature ovarian failure or premature menopause). It can occur naturally or as a result of medical or surgical treatment.
Early menopause	Menopause occurring between ages 40-44.
Urogenital atrophy	Thinning and shrinking of the tissues of the vulva, vagina, urethra and bladder caused by oestrogen deficiency. This results in multiple symptoms such as vaginal dryness, vaginal irritation, a frequent need to urinate and urinary tract infections.
Vasomotor symptoms	Menopausal symptoms such as hot flushes and night sweats caused by constriction and dilatation of blood vessels in the skin that can lead to a sudden increase in blood flow to allow heat loss. These symptoms can have a major impact on activities of daily living.

Notes

The choice of HRT for an individual depends on an overall balance of indication, risk-benefit profile, side effects and convenience. Prescribe the lowest effective dose of HRT for the shortest time possible.

Start at a low dose especially in older women (may be less tolerant of oestrogen) and increase if symptoms persist after a few months. Tailor the dose to the symptoms, as the ingested or applied dose may not be well absorbed.

Low dose	estradiol 0.5mg/1mg, conjugated oestrogens 300mcg, estradiol patch 25 /37.5mcg
Standard dose	estradiol 2mg, conjugated oestrogens 625mcg, estradiol patch 50mcg, oestrogel 2 measures
High dose	estradiol patch 75/100mcg, oestrogel 4 measures, conjugated oestrogens 1.25mg

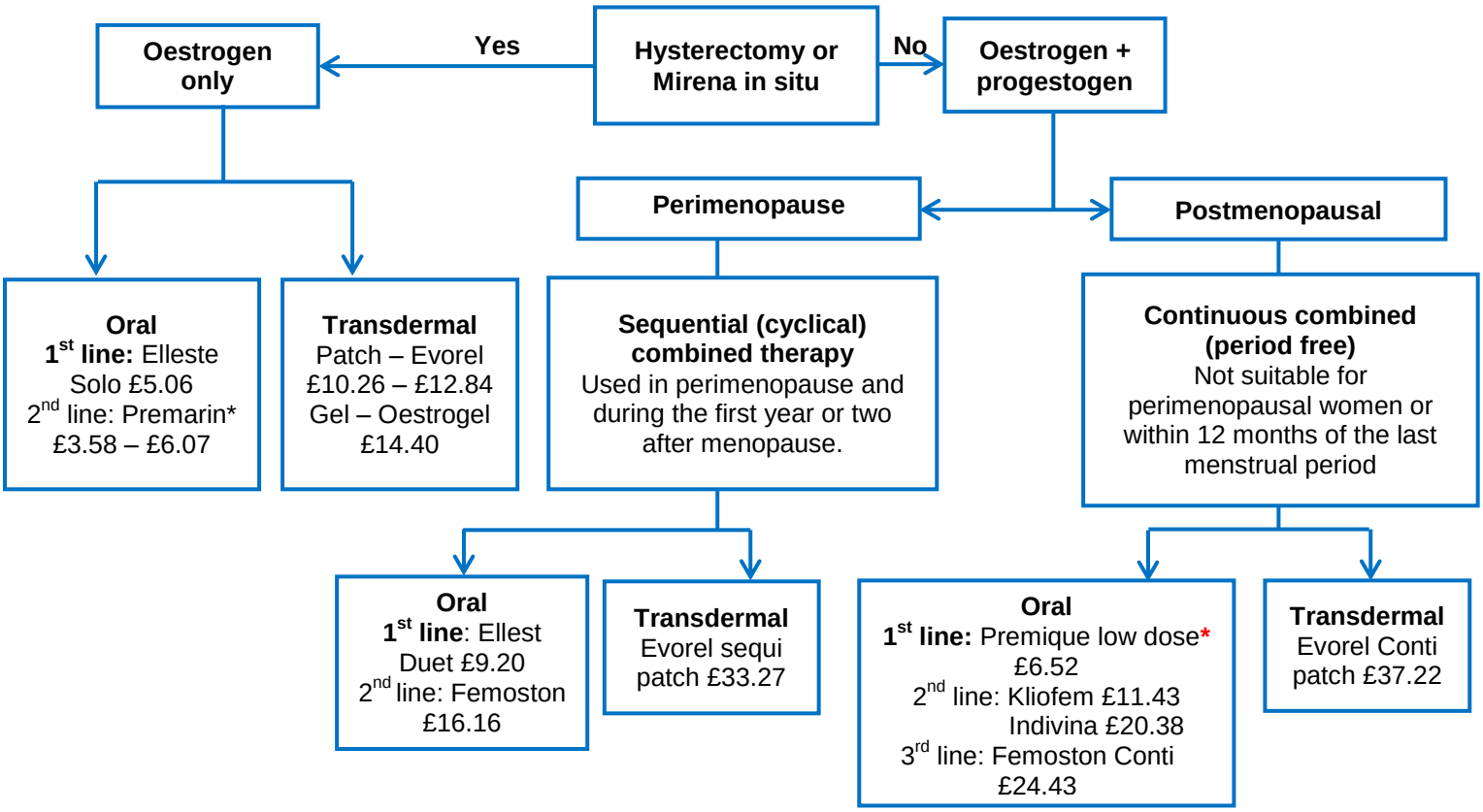
Side effects tend to be related to the progestogen component of combined HRT.

Progestogenic side effect may include PMS type symptoms, breast tenderness, lower abdominal pain, backache, depressed mood, acne/greasy skin, headache.

If androgenic or PMS side effects occur on C19 progestogens (levonorgestrel/norethisterone), advise change to C21 progestogen (dydrogesterone/medroxyprogesterone). If side effects are still unacceptable, consider Mirena Intrauterine system.

Formulary choice of HRT

(Flow chart adapted from BMS society HRT guideline https://thebms.org.uk/_wprs/wp-content/uploads/2016/04/HRT-Guide-160516.pdf)



*the oestrogen in Premarin and Premique is horse oestrogen (from pregnant horse urine), these may not be acceptable to all women; all other preparations in which the oestrogens are identical to human oestrogens

Patches are more expensive than oral preparations but may be **suitable for patients with high risk of VTE** (e.g. those with a BMI over 30 kg/m^2). Consider referring those at high risk (strong family history of VTE or a hereditary thrombophilia) to a haematologist for assessment before considering HRT.

Transdermal routes avoid the first pass effect through the liver and are not associated with increased low density lipoproteins, venous thrombosis or stroke. Patches deliver a more steady level of hormone which can be helpful in conditions triggered by fluctuating levels eg migraine.

Hormonal content of formulary HRT preparations (Prices as per MIMs February 2018)

OESTROGEN ONLY	Formulation	Oestrogen	Strength	Progestogen	3months cost
Elleste Solo	1st line tablet	Estradiol	1mg 2mg	--	£5.06 £5.06
Premarin*	2nd line tablet	Conjugated oestrogens	300mcg 625mcg 1.25mg	--	£6.07 £4.02 £3.58
Evorel	24h patch	Estradiol	25mcg 50mcg 75mcg 100mcg	--	£10.26 £11.66 £12.36 £12.84
Oestrogel	Gel	Estradiol	0.06%	--	£12.6-£25.2
SEQUENTIAL COMBINED	**Formulation**	**Oestrogen**	**Strength**	**Progestogen**	**Cost for 3 months**
Elleste Duet	1st line tablet	Estradiol	1mg 2mg	Norethirsterone 1mg	£9.20 £9.20
Femoston	2nd line tablet	Estradiol	1mg 2mg	Dydrogesterone 10mg	£16.16 £16.16
Evorel sequi	Patch	Estradiol	50mcg	Norethisterone 170mcg	£33.27
CONTINUOUS COMBINED	**Formulation**	**Oestrogen**	**Strength**	**Progestogen**	**Cost for 3 months**
Premique low dose*	1st line tablet	Conjugated oestrogens	300mcg	Medroxyprogesterone 1.5mg	£6.52
Kliofem	2nd line tablet	Estradiol	2mg	Norethisterone 1mg	£11.43
Indivina				Medroxyprogesterone 2.5mg or 5mg	£20.38
Femoston conti	3rd line tablet	Estradiol	0.5mg, 1mg	Dydrogesterone 2.5mg, 5mg	£24.43
Evorel Conti	Patches	Estradiol	50mcg/24hr	Norethisterone 170mcg	£37.22

Mirena

Mirena is a levonorgestrel-releasing intrauterine system (IUS) for use in combination with oestrogen as the progestogen element of sequential or continuous combined HRT. It is licensed for 4 years for this indication, as oppose to 5 years when used solely for contraception. This is particularly useful for women who experience heavy bleeding on sequential preparation, require contraception or suffer unacceptable side effects from the progestogen element of HRT.

Tibolone

Tibolone is a synthetic steroidal compound with oestrogenic, progestogenic, and androgenic activity.
It is licensed for the treatment of oestrogen deficiency symptoms in postmenopausal women (more than 1 year after menopause) and an option for postmenopausal women where progestin-containing therapy is not appropriate (eg. progestogenic adverse effects). See MHRA information on risk vs benefit.

Further information

NICE NG23 Menopause: diagnosis and management https://www.nice.org.uk/guidance/ng23.

- 'Information for Patients' which suggests points that women may find helpful to discuss with their doctor or nurse http://www.nice.org.uk/guidance/ng23/informationforpublic.
- Summary of the key messages NICE Bites

Other relevant NICE guidelines

- CG80 Early and locally advanced breast cancer CG80 and
- CG164 Familial breast cancer.

These include advice to stop HRT if breast cancer is diagnosed. HRT may, in exceptional cases, be offered to women with a history of breast cancer with severe menopausal symptoms and with whom the associated risks have been discussed. Advice to individual women with a family history of breast cancer on the use of HRT should vary according to the individual clinical circumstances (such as age, severity of menopausal symptoms, or osteoporosis).

British Menopause Society (BMS) https://thebms.org.uk/nice-guideline/overview/

- Tool for clinicians including NICE NG23 Guideline Summary & HRT Guide
- Factsheet on 'migraine and HRT' useful in managing perimenopausal women with migraine.

Reference

NICE NG23 Menopause November 2015 https://www.nice.org.uk/guidance/ng23.
The British Menopause Society http://www.thebms.org.uk/
Clinical Knowledge Summaries Accessed January 2018 https://cks.nice.org.uk/menopause

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Document update	Date updated
Mirena licencing information added	February 2018
Contact section removed as local specialist menopause service decommissioned	February 2019

Appendix 1: Absolute risks of HRT (NICE NG23)

Table 1: Absolute rates of coronary heart disease for different types of HRT compared with no HRT (or placebo), different durations of HRT use and time since stopping HRT for menopausal women

		Difference in coronary heart disease incidence per 1000 menopausal women over 7.5 years (95% confidence interval) (baseline population risk in the UK over 7.5 years: 26.3 per 1000 [1])			
		Current HRT users	Treatment duration <5 years	Treatment duration 5–10 years	>5 years since stopping treatment
Women on oestrogen alone	RCT estimate[2]	6 fewer (-10 to 1)	No available data	No available data	6 fewer (-9 to -2)
	Observational estimate[3]	6 fewer (-9 to -3)	No available data	No available data	No available data
Women on oestrogen + progestogen	RCT estimate[2]	5 more (-3 to 18)	No available data	No available data	4 more (-1 to 11)
	Observational estimate[3]	No available data	No available data	No available data	No available data

HRT, hormone replacement therapy; RCT, randomised controlled trial
For full source references, see Appendix M in the full guideline.
[1] Results from Weiner 2008 were used for the baseline population risk estimation.
[2] For women aged 50–59 years at entry to the RCT.
[3] Observational estimates are based on cohort studies with several thousand women.

Table 2: Absolute rates of stroke for different types of HRT compared with no HRT (or placebo), different durations of HRT use and time since stopping HRT for menopausal women

		Difference in stroke incidence per 1000 menopausal women over 7.5 years (95% confidence interval) (baseline population risk in the UK over 7.5 years: 11.3 per 1000 [1])			
		Current HRT users	Treatment duration <5 years	Treatment duration 5–10 years	>5 years since stopping treatment
Women on oestrogen alone	RCT estimate[2]	0 (-5 to 10)	No available data	No available data	1 more (-4 to 9)
	Observational estimate[3]	3 more (-1 to 8)	No available data	No available data	No available data
Women on oestrogen + progestogen	RCT estimate[2]	6 more (-2 to 21)	No available data	No available data	4 more (-1 to 13)
	Observational estimate[3]	4 more (1 to 7)	No available data	No available data	No available data

HRT, hormone replacement therapy; RCT, randomised controlled trial
For full source references, see Appendix M in the full guideline.
[1] Results from Weiner 2008 were used for the baseline population risk estimation.
[2] For women aged 50–59 years at entry to the RCT.
[3] Observational estimates are based on cohort studies with several thousand women.

Table 3: Absolute rates of breast cancer for different types of HRT compared with no HRT (or placebo), different durations of HRT use and time since stopping HRT for menopausal women

		Difference in breast cancer incidence per 1000 menopausal women over 7.5 years (95% confidence interval) (baseline population risk in the UK over 7.5 years: 22.48 per 1000 [1])			
		Current HRT users	Treatment duration <5 years	Treatment duration 5–10 years	>5 years since stopping treatment
Women on oestrogen alone	RCT estimate[2]	4 fewer (-11 to 8)	No available data	No available data	5 fewer (-11 to 2)
	Observational estimate[3]	6 more (1 to 12)[4]	4 more (1 to 9)	5 more (-1 to 14)	5 fewer (-9 to -1)
Women on oestrogen + progestogen	RCT estimate[2]	5 more (-4 to 36)	No available data	No available data	8 more (1 to 17)
	Observational estimate[3]	17 more (14 to 20)	12 more (6 to 19)	21 more (9 to 37)	9 fewer (-16 to 13)[5]

HRT, hormone replacement therapy; RCT, randomised controlled trial
For full source references, see Appendix M in the full guideline.
[1] Office for National Statistics (2010) breast cancer incidence statistics.
[2] For women aged 50–59 years at entry to the RCT.
[3] Observational estimates are based on cohort studies with several thousand women.
[4] Evidence on observational estimate demonstrated very serious heterogeneity without plausible explanation by subgroup analysis.
[5] Evidence on observational estimate demonstrated very serious imprecision in the estimate of effect.

Table 4: Absolute rates of any fragility fracture for HRT compared with no HRT (or placebo), different durations of HRT use and time since stopping HRT for menopausal women

		Difference in any fragility fracture incidence per 1000 menopausal women (95% confidence interval) (see footnotes for information on baseline population risk and length of follow-up time over which absolute risk difference is calculated)			
		Current HRT users	Treatment duration <5 years	Treatment duration 5–10 years	>5 years since stopping treatment
Women on any HRT	RCT estimate[1]	23 fewer (-10 to -33)[3]	25 fewer (-9 to -37)[4]	No available data	No available data
	Observational estimate[2]	16 fewer (-15 to -18)[5]	15 fewer (-11 to -17)[5]	18 fewer (-15 to -20)[5]	2 more (-19 to 27)[6]

HRT, hormone replacement therapy; RCT, randomised controlled trial
For full source references, see Appendix M in the full guideline.
Absolute risks calculated by using the baseline population risk in the control arm for each analysis, following GRADE methodology.
[1] For women aged 50–59 years at entry to the RCT.
[2] Observational estimate is based on cohort studies with several thousand women.
[3] Baseline population risk = 69 per 1000 women (follow-up: 3.43 years).
[4] Baseline population risk = 78 per 1000 women (follow-up: 3.71 years).
[5] Baseline population risk = 15.4 per 1000 women (follow-up: 2.8 years).
[6] Baseline population risk = 106 per 1000 women (follow-up: 5 years).