GUIDANCE FOR MANAGING THE MENOPAUSE

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<table>
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<tr>
<th>Approved on behalf of the:</th>
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<tbody>
<tr>
<td>North of Tyne and Gateshead Medicines Guidelines and Use Group</td>
<td></td>
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<tr>
<td>North of Tyne Area Prescribing Committee</td>
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<table>
<thead>
<tr>
<th>Review date</th>
<th>July 2019</th>
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| Organisations signed up to this guideline | Newcastle Gateshead CCG, North Tyneside CCG, Northumberland CCG, Gateshead Health NHS Foundation Trust, Newcastle upon Tyne Hospitals NHS Foundation Trust, Northumbria Healthcare Foundation Trust |

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<thead>
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<th>Name of originator/author</th>
<th>Diana Mansour</th>
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2017
North of Tyne and Gateshead

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1. Introduction to the guidance

This guidance is intended to inform all clinicians in the Newcastle, North Tyneside, Northumberland and Gateshead areas involved in managing women with troublesome menopausal problems. It has been developed as a consensus between representatives from primary and secondary care, with reference to national guidelines, including from NICE, MHRA and the British Menopause Society. It is intended to guide clinical management, but every woman should be assessed and managed individually.

1.1 How to use this guidance

This guidance starts with an algorithm for prescribing hormone replacement therapy and is followed by a chart containing formulary products used to treat menopausal symptoms. This is followed by more detailed information outlining the management of menopausal symptoms with hyperlinks to the BNF, local osteoporosis guidance, MHRA warnings and statements, NICE documents as appropriate.

1.2 Off-label prescribing

This guidance mentions ‘off-label prescribing’. There are clinical situations when the use of unlicensed medicines or use of medicines outside the terms of the licence (‘off-label’) may be judged by the prescriber to be in the best interest of the patient on the basis of available evidence.

Healthcare professionals may advise on the use of an unlicensed medicine when no licensed suitable alternative is available. Prescribers should pay particular attention to the risks associated with using unlicensed medicines or using a licensed medicine off-label.

- Before prescribing an unlicensed medicine, be satisfied that an alternative, licensed medicine would not meet the patient’s needs
- Before prescribing a medicine off-label, be satisfied that such use would better serve the patient’s needs than an appropriately licensed alternative

Before prescribing an unlicensed medicine or using a medicine off-label:

- be satisfied that there is a sufficient evidence base and/or experience of using the medicine to show its safety and efficacy
- take responsibility for prescribing the medicine and for overseeing the patient’s care, including monitoring and follow-up
- record the medicine prescribed and, where common practice is not being followed, the reasons for prescribing this medicine; you may wish to record that you have discussed the issue with the patient

Communicate: best practice is that...

- You give patients, or those authorising treatment on their behalf, sufficient information about the proposed treatment, including known serious or common adverse reactions, to enable them to make an informed decision
- Where current practice supports the use of a medicine outside the terms of its licence, it may not be necessary to draw attention to the licence when seeking consent. However,
it is good practice to give as much information as patients or carers require or which they may see as relevant

- You explain the reasons for prescribing a medicine off-label or prescribing an unlicensed medicine where there is little evidence to support its use, or where the use of a medicine is innovative


1.3 Discontinuation of Premarin products

Prempak C and Premique have been discontinued by the Pfizer for economic reasons. Premique low dose (conjugated oestrogens 300 mcg with medroxyprogesterone acetate 1.5mg daily) is still available.

Alternative oral preparations include Elleste Duet 1mg which is equivalent to 0.625mg Prempak C.

Elleste Duet 2mg is equivalent to 1.25mg Prempak C.

An alternative to Premique would be a continuous combined preparation such as Kliovance that contains estradiol 1mg and norethisterone acetate 500mcg daily.
1.4 Algorithm for hormone replacement therapy prescribing

**Without Uterus**

**Estrogen only**

Offer women low dose tablet or non-oral if preferred (0.3mg CEE or 1mg estradiol or 25mcg patch)

**Symptoms persist at 3 months – increase dose (0.625mg CEE or 2mg estradiol or 50mcg patch)**

**Symptoms persist after further 3 months**

Consider increasing dose to 1.25mg CEE or 75mcg patch and referral to menopause clinic if problems persist

**With Uterus**

Menopausal assessment including symptoms, relevant history, risk/benefit analysis

**< 1 year since last natural period at any age**

Low dose cyclical HRT (1mg estradiol + progestogen)

**Symptoms persist at 3 months**

Standard dose cyclical HRT (2mg estradiol + progestogen or 0.625mg CEE + progestogen or 50mcg patch + progestogen)

**Symptoms persist at 3 months**

Higher dose cyclical HRT (1.25mg CEE + progestogen)

**Post-menopausal 1 year since last natural period at any age**

Low dose continuous combined HRT (1mg estradiol + progestogen or 0.3mg CEE + progestogen or tibolone)

**Symptoms persist at 3 months**

Change to continuous combined HRT 1 year after LMP if over 50 or after several years if under 50

**Irregular bleeding more than 6 months**

Refer to Gynaecologist
1.5 Hormone Replacement Therapy (HRT) – Products on North of Tyne and Gateshead Formulary

<table>
<thead>
<tr>
<th>Type</th>
<th>Brand</th>
<th>Oestrogen</th>
<th>Progestogen</th>
<th>Formulation</th>
<th>Bleed</th>
<th>RX*</th>
<th>Cost</th>
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</thead>
<tbody>
<tr>
<td>Sequential Therapy</td>
<td>Elleste Duet</td>
<td>Estradiol (1mg or 2mg)</td>
<td>Norethisterone (1mg)</td>
<td>Tabs</td>
<td>M</td>
<td>2</td>
<td>£9.20 (3x28 tab)</td>
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<tr>
<td></td>
<td>Evorel Segui</td>
<td>Estradiol (50 micrograms)</td>
<td>Norethisterone (170micrograms)</td>
<td>Patches</td>
<td>M</td>
<td>2</td>
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<td>Femoston</td>
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<td>Dydrogesterone (10mg)</td>
<td>Tabs</td>
<td>M</td>
<td>2</td>
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<td>Continuous combined therapy</td>
<td>Evorel Conti</td>
<td>Estradiol (50micrograms)</td>
<td>Norethisterone (170micrograms)</td>
<td>Patches</td>
<td>X</td>
<td>1</td>
<td>£13.00 (8 patch) £37.22 (24 patch)</td>
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<td>Kliofem</td>
<td>Estradiol (2mg)</td>
<td>Norethisterone (1mg)</td>
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<td>X</td>
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<td>£11.43 (3x28 tab)</td>
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<td>Kliovance</td>
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<td>Norethisterone (0.5mg)</td>
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<td></td>
<td>Premique Low Dose</td>
<td>Conj. oestrogen (300micrograms)</td>
<td>Medroxyprogesterone (1.5mg)</td>
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<td>Livial</td>
<td>Tibolone (2.5mg)</td>
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<tr>
<td>Type</td>
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<td>Progestogen</td>
<td>Formulation</td>
<td>Bleed</td>
<td>RX*</td>
<td>Cost</td>
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<tr>
<td><strong>Unopposed oestrogen (if uterus is intact an adjunctive progestogen must be used)</strong></td>
<td></td>
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<td></td>
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<tr>
<td><strong>Evorel</strong></td>
<td></td>
<td>Estradiol</td>
<td>(25microgram or 50microgram or 75microgram or 100microgram)</td>
<td>Patches</td>
<td></td>
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<td>£3.42, £3.88, £4.12, £4.28 (all 8 patch pack)</td>
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<tr>
<td><strong>Premarin</strong></td>
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<td>Conj. oestrogen 300 microgram or 625 microgram or 1.25mg)</td>
<td>Tabs</td>
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<td>£6.07, £4.02, £3.58 (all 3 x28 tab)</td>
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<tr>
<td><strong>Progynova TS</strong></td>
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<td>Estradiol (50microgram or 100microgram)</td>
<td>Patches</td>
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<td>1</td>
<td>£18.90 £20.70 (12 patch pack)</td>
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<td><strong>Sandrena</strong></td>
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<td>Estradiol (0.1%) (500microgram/500mg, 1mg/1g)</td>
<td>Gel</td>
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<td>£5.08, £5.85 (28 sachet pack)</td>
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<td><strong>Elleste Solo</strong></td>
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<td>Estradiol 1mg, 2mg</td>
<td>Tabs</td>
<td></td>
<td>1</td>
<td>£5.06 £5.06</td>
<td></td>
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<tr>
<td><strong>Adju stream progestogen</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td><strong>Mirena</strong></td>
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<td>Levonorgestrel (20mcg/24hrs)</td>
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<td><strong>Provera</strong></td>
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<td>Medroxyprogesterone (2.5mg) (5mg) (10mg)</td>
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<td>1</td>
<td>£1.84 £1.23 £2.47</td>
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<tr>
<td><strong>Vaginal estrogen only</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Gynest</strong></td>
<td></td>
<td>Estriol (0.01%)</td>
<td>Vaginal cream</td>
<td></td>
<td></td>
<td>1</td>
<td>£4.67</td>
</tr>
<tr>
<td><strong>Estriol cream</strong></td>
<td></td>
<td>Estriol (0.1%)</td>
<td>Vaginal cream</td>
<td></td>
<td></td>
<td>1</td>
<td>£4.45</td>
</tr>
<tr>
<td><strong>Vagifem</strong></td>
<td></td>
<td>Estradiol (10microgram)</td>
<td>Vaginal tabs</td>
<td></td>
<td></td>
<td>1</td>
<td>£16.72 (24 tablets)</td>
</tr>
</tbody>
</table>

Bleed: M=Monthly; Q=Quarterly; X=No bleed  *Combination packs incur multiple prescription charges Cost=28 days

**Source:** BNF, 2014
2. About the menopause

The average age of the menopause in the UK is 51 years:

- symptoms last on average for 2-5 years
- at least 10% of women will still be symptomatic 10 years after their last natural period
- 80% of women experience menopausal symptoms which include hot flushes, night sweats, insomnia, memory problems, poor concentration, lethargy, mood changes (low mood), joint and muscle pains and stiffness, urinary symptoms, vaginal dryness and loss of libido
- 45% of women find their menopausal symptoms distressing
- about 20% of symptomatic women will request help
- symptoms typically last 4 years after the final period with about 10% of women experiencing symptoms for up to 12 years.

An early menopause occurs before the age of 45 and premature menopause before the age of 40 years. Overall incidence is thought to be:

- 5% women between 40 and 45#
- 1% of women younger than 40 years #
- 0.1% of those under 30 years#

The causes of premature menopause are listed in table 1. Women with premature menopause are at increased risk of developing osteoporosis and cardiovascular disease.

- There is an 80% increased risk of ischaemic heart disease in women with a menopause before the age of 40 compared to those with a menopause at 49-50 years of age.
- Women with premature menopause have significantly lower bone mineral density compared with controls and may have up to 50% increased risk of fracture.

<table>
<thead>
<tr>
<th>Causes of premature menopause</th>
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<tr>
<td><strong>Primary</strong></td>
</tr>
<tr>
<td>- Chromosome abnormalities</td>
</tr>
<tr>
<td>- Follicle stimulating hormone receptor gene polymorphism and inhibin B mutation</td>
</tr>
<tr>
<td>- Enzyme deficiencies</td>
</tr>
<tr>
<td>- Autoimmune disease</td>
</tr>
<tr>
<td><strong>Secondary</strong></td>
</tr>
<tr>
<td>- Chemotherapy and radiotherapy</td>
</tr>
<tr>
<td>- Bilateral oophorectomy or surgical menopause</td>
</tr>
<tr>
<td>- Hysterectomy without oophorectomy</td>
</tr>
<tr>
<td>- Infection</td>
</tr>
</tbody>
</table>
3. Indications for HRT

HRT is indicated:
- for the management of menopausal vasomotor and urogenital symptoms - 77% reduction in vasomotor symptoms compared to placebo in clinical trials
- for women with an early menopause (below 45 years) to prevent osteoporosis, and should normally be continued until the average age of the menopause (51 years)
- for prevention and treatment of osteoporosis in women over 50 years, with menopausal symptoms

[Supplied link]

4. Contraindications

The following situations are absolute contraindications to the prescribing of HRT:
- history of breast cancer
- active endometrial cancer
- active venous thromboembolism
- active cardiovascular disease
- undiagnosed vaginal bleeding
- uncontrolled hypertension

Extra caution should be exercised in the following situations and advice sought from local specialists:
- previous venous thromboembolism
- previous cardiovascular disease
- endometrial cancer or other oestrogen dependent cancer
- active liver disease

Women taking HRT, who undergo elective surgery should discuss the continuation of their medication with their surgeon. Most surgeons would advise that HRT can be continued but such women may require VTE prophylaxis.

[Supplied link]

5. Initial Consultation

This requires time and should include:
- current symptoms (need to consider if these symptoms are likely to respond to HRT)
- menstrual history including last menstrual period, frequency, heaviness and duration of periods, any postmenopausal or post-coital bleeding
- past medical history and relevant family history - explore risk factors for
osteoporosis, breast cancer and coronary heart disease

• assess woman's knowledge and expectations
• lifestyle advice particularly smoking, alcohol, exercise, diet
• teach breast awareness
• balanced counselling with regard to HRT explaining the risks and benefits
• discuss non-hormonal options and non-pharmaceutical options, for example cognitive behavioural therapy (CBT)
• up to date patient information leaflets
• prescribe three months of HRT – explain that unscheduled bleeding in women with a uterus is common in the first 3 months of HRT use
• contact telephone number

5.1 Investigations

• blood pressure as a baseline
• body mass index as a baseline
• check entry into breast screening programme, if over 50 years old
• cervical cytology, if indicated by cervical screening programme
• pelvic examination, only if symptoms are present
• full blood count, thyroid function, lipid profile etc. depending on the presenting history or symptoms or as part of a CVD risk assessment

6. Diagnosing the menopause

Diagnosis of menopause is usually based on clinical assessment. NICE recommend making the diagnosis in women over the age of 45 on the basis of their presentation with vasomotor symptoms and irregular periods or an absence of a period for at least 12 months (providing she is not using a hormonal method of contraception).

Blood tests:

• there is little place for the routine measurement of FSH, LH or estradiol
• there is no specific biological marker for the menopause
• women may suffer from vasomotor symptoms but have normal blood test results
• it may be useful to check FSH in women under 45 with atypical symptoms or if you need to confirm menopause in women using progestogen-only contraception/after a hysterectomy with conservation of ovaries

If FSH is measured:

• blood should be taken within the first 3 days of the menstrual cycle or two weeks apart if amenorrhoeic
• serum estradiol levels may be useful in ‘symptomatic’ patients using non-oral therapy

A diagnosis of premature menopause can be made in women aged under 40 in the presence of menopausal symptoms including infrequent or absent periods and an elevated FSH (>30IU/L)
on two blood samples taken 4-6 weeks apart.

7. Contraception and the menopause

HRT is not a contraceptive. Menopausal women over the age of 50:
- should use a contraceptive method for one year following their last natural menstrual period

Menopausal women under 50:
- should use a contraceptive method for 2 years following their last natural menstrual period as breakthrough ovulation can occur

Women starting HRT before cessation of menstruation should still use contraception
- FSH is not greatly suppressed by oral or transdermal HRT therefore can be measured
- a woman is likely to be menopausal if two FSH levels are >30IU/L (first sample should be taken within 3 days of the start of a withdrawal bleed and a second two weeks later).

Perimenopausal women taking combined hormonal contraception (CHC)
- may develop vasomotor symptoms in the pill-free interval
- should normally be changed from a CHC to a progestogen-only method at the age of 50
- have suppressed FSH levels - FSH levels are not affected by progestogen-only methods including progestogen injectables

In women who are amenorrhoeic using progestogen-only contraceptive methods:
- one POP is not sufficient to provide endometrial protection
- contraception can be continued until 55 years of age
- those using a progestogen-only injectable can be converted to another method by the age of 50 but may wish to continue with this method

For those using an IUS containing 52mg levonorgestrel (LNG 52-IUS):
- if fitted after the age of 45 it can remain in place for 7 years. If at 52 the woman is amenorrhoeic it can remain in place until she is 55 when most women are one year after their last natural period. If she is having bleeds after 7 years then it should be changed.
- if treatment of menopausal symptoms is required estradiol can be added, with the progestogenic component of HRT being supplied by the LNG 52-IUS providing a continuous combined method. LNG 52-IUS should be changed every 5 years when used with estrogen replacement therapy (off-licensed use but recommended by FSRH).

Alternatively in those using progestogen-only contraceptive methods
- if the FSH is 30 IU/L or more, it should be repeated in 2 weeks
- if the second FSH is again raised (above 30 IU/L) it is likely that the woman is menopausal and contraception should be continued for the next 2 years if under 50 or one year if over 50
- if levels are less than 30 IU/L FSH can be measured again in 12 months time
8. Hormone Replacement Therapy

The type of HRT used is determined by the presence or absence of a uterus, menopausal status, past medical history and current medication. Generally women who have had a hysterectomy are offered estrogen replacement therapy (ERT) whilst those with an intact uterus are prescribed estrogen with a progestogen given sequentially or continuously.

8.1 Sequential HRT:

- should be prescribed if a woman’s last menstrual period was less than one year ago
- contains 28 days of continuous estrogen and 10-14 days of progestogen
- should be started at a low dose (containing 1mg estradiol) and increased after 3 months until symptoms are not controlled
- produces bleeding at a regular, predictable time each month however the onset may vary between preparations
- women who are amenorrhoeic using a progestogen-only method need to be informed they are likely to experience a monthly bleed once they commence HRT

Absence of bleeding occurs in approximately 5 % of women and requires no further investigation provided that:

- symptoms are controlled
- the progestogen component is being taken
- there is no irregular bleeding

Minimum daily progestogen doses for a sequential regimen to prevent endometrial hyperplasia are:

- 10 mg dydrogesterone
- 75 μg levonorgestrel
- LNG 52-IUS
- 10 mg medroxyprogesterone acetate
- 0.7 mg norethisterone
- 150 μg norgestrel
- 90 mg progesterone vaginal gel (alternate days)
- 200 mg micronised progesterone

8.2 Long cycle HRT:

- contains 70, 2mg estradiol valerate tablets, 14 2mg estradiol valerate and 20 mg medroxyprogesterone acetate tablets as well as 7 placebo tablets
- produces four withdrawal bleeds per year
- may cause initial irregular bleeding in the first two treatment cycles (6 months) but this tends to settle

Endometrial hyperplasia has been reported when lower doses of progestogen are used for 10
days of an 84-day cycle.

8.3 Continuous combined HRT:

- contains continuous estrogen and progestogen to induce endometrial atrophy and decrease the risk of endometrial hyperplasia and cancer
- can be prescribed for postmenopausal women to avoid monthly bleeds
- is indicated for postmenopausal women

Women who start sequential HRT before their periods stop may consider changing to a continuous combined therapy after several years of sequential HRT if under 50 or 12 months if over 50.

Low dose continuous combined HRT (containing 1mg estradiol or 300 micrograms conjugated equine estrogens):

- controls menopausal symptoms
- is bone protective
- gives less erratic bleeding
- results in fewer side-effects than higher dose preparations

Switching from sequential HRT to continuous combined HRT:

- switch at the end of a withdrawal bleed, when the endometrium is at its thinnest
- most women experience some light bleeding/spotting during the first 3-6 months of treatment with more than 75% becoming amenorrhoeic after 6 months use

Tibolone is a selective estrogen receptor modulator

- with estrogenic, progestogenic and androgenic actions
- with the same indications and contraindications for use as continuous combined HRT
- and used when additional effects for improving libido and less initial bleeding/spotting/breast tenderness is desired
- but is a more expensive option

8.4 ERT (estrogen replacement therapy):

- is for use in women who have had a hysterectomy
- can be given as a tablet, patch or gel
- may have less adverse effects on the breast

9. HRT use in specific circumstances

9.1 Premature ovarian insufficiency (POI)

HRT is recommended for women with premature menopause and continued until the average
age of natural menopause.

- this may be achieved with sequential HRT or combined hormonal contraceptive (providing there are no contraindications) or estrogen alone if the woman has undergone a hysterectomy. All will provide bone protection.
- there is little data to suggest one option should be used in preference to the other, however psychologically combined hormonal contraception (CHC) may be preferred
- women with POI often need a higher dose of estrogen than women in their 50s, dose should be titrated to symptoms
- the aim is to maintain hormone levels close to physiological levels
- for women using CHC as hormone replacement, symptoms may reoccur in the hormone-free interval (HFI), therefore tricycling CHCs, reducing the HFI or taking HRT may be of benefit
- there is no evidence that HRT increases the risk of breast cancer in women under 50 to a level greater than that found in normally menstruating women
- HRT is important to preserve uterine function in women planning ovum donation
- testosterone may be considered for treating reduced libido (especially in oophorectomized women); however seek specialist advice before prescribing these preparations

9.2 Women with a uterus

The addition of sequential or continuous progestogen to estrogen is required to prevent endometrial hyperplasia with its associated risk of endometrial cancer:

- in women with a uterus
- in women after endometrial ablation

9.3 Women following subtotal hysterectomy

In women following a subtotal hysterectomy, endometrium may remain in the cervical stump. To reduce the risk of endometrial hyperplasia a progestogen challenge is advised using 3 months of sequential HRT:

- if a withdrawal bleed occurs then a continuous combined HRT preparation is advised
- if there is no bleed then ERT can be given

9.4 Women without a uterus

ERT can be used in women who have had a hysterectomy:

- start with a low dose e.g. 1mg estradiol or a 25µg patch
- increase the dose at 3 months to control symptoms

9.5 Women following hysterectomy for endometriosis

In those women wishing to use HRT after hysterectomy and bilateral oophorectomy for endometriosis

- combined HRT is advisable for the first year
- conversion to ERT is recommended from year two onwards owing to a
10. Choice of regimen

First line therapy is usually oral due to lower cost and user preference. Transdermal oestrogen is associated with fewer risks than oral HRT at low doses.

Non-oral HRT (patch, gel,) has less effect on clotting factors and reduces triglyceride levels. They are useful in women:

- have an individual preference
- with poor symptoms control when taking oral HRT
- with nausea, headaches or breast tenderness caused by oral HRT
- with malabsorption problems
- with lactose intolerance
- with a history of gallstones
- who take liver enzyme-inducing drugs e.g. carbamazepine
- at risk of venous thromboembolism (VTE)
- with liver disease
- with migraine
- with diabetes
- with hypertension and other cardiovascular risk factors

Topical estrogen:

- is indicated as first line therapy for women with vaginal atrophy
- can be used in conjunction with systemic HRT
- may be used in women for whom systemic HRT is contraindicated following advice from a clinician with expertise in menopause management
- it should be continued for as long as needed to manage symptoms as these will return once the preparation is stopped
- topical estrogen cream, pessaries and vaginal rings are all equally effective
- vaginal administration results in minimal systemic absorption and therefore very few side effects
- women should be advised to attend for review if they experience any unscheduled vaginal bleeding

LNG 52-IUS plus an estrogen may be used:

- if progestogen side effects are experienced with other formulations
- if contraception is still required or a LNG 52-IUS was in place before ERT was commenced
- if there is persistently heavy bleeding when taking sequential HRT (providing investigations are normal)
- at the request of the women seeking HRT

10.1 Estrogen dose equivalents

There is no published evidence related to different estrogens and their equi-potency. However, it is generally thought that the following preparations are approximately equivalent although
their clinical effects are dependent upon the progestogen within the combination.

**Very Low Dose**
- 0.5 mg estradiol
- 300 micrograms conjugated equine estrogens
- 25 microgram matrix patch cut in half (off-label)

**Low Dose**
- 1 mg estradiol
- 0.5 mg estradiol gel
- 25 microgram patch
- 2.5 mg tibolone

**Standard Dose**
- 2 mg estradiol
- 625 micrograms conjugated equine estrogens
- 1 mg estradiol gel
- 50 microgram patch

**High Dose**
- 1.25 mg conjugated equine estrogens
- 75 microgram patch
- 100 microgram patch

10.2 Progestogens that can be used with ERT

The progestogens currently available as adjuncts to estrogen for endometrial protection are:
- micronised progestogen 200mg tablets taken for 14 days in a 28 day cycle or 100mg taken daily to provide a continuous combined formulation
- Medroxyprogesterone acetate 10mg for 12-14 days in a 28 day cycle or 5mg daily to provide a continuous combined formulation
- LNG 52-IUS providing a continuous combined HRT

10.3 Testosterone

At present, there is no licensed product for women as testosterone patches and implants have been withdrawn for commercial reasons. North of Tyne and Gateshead APC have not approved the use of testosterone in women. [http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON087990](http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON087990)

In studies testosterone supplementation may help improve libido in women who have undergone bilateral oophorectomy. NICE recommend testosterone supplementation for menopausal women with low sexual desire when HRT alone is not effective.
- women should also take systemic HRT as safety data relates to studying women taking testosterone with HRT
- An ‘off-label’ testosterone gel option is using one sachet or tube of gel over 7-10
days (Testogel 50mg/5g sachet or Testim 50mg/5g tube)
• levels are monitored every 2 weeks until these are stable
• testosterone levels should be kept between 1-2 nmol/L

11. Side-effects

HRT side-effects can be related to either the estrogen or progestogen component with progestogenic side-effects being more common.

11.1 Estrogenic side-effects

Estrogenic side-effects:
• include fluid retention, bloating, nausea, headaches, breast tenderness, leg cramps
• are normally transient and will usually subside after 3 months
• may be more problematic in those who are some years passed their menopause

If these symptoms persist:
• reduce the dose of estrogen
• change the route of administration e.g. from oral to patch
• take medication with food

11.2 Progestogenic side-effects

Progestogenic side-effects:
• occur cyclically in those using sequential HRT
• include premenstrual symptoms (fluid retention, bloating, irritability, depression, breast tenderness)
• include androgenic effects (acne, greasy skin, facial hair)
• include headaches or migraine
• are normally transient and will usually subside after 3 months

If progestogenic side-effects persist:
• consider changing the progestogen to micronised progesterone or similar
• consider long cycle HRT
• consider a transdermal/vaginal progestogen or tibolone

12. Follow up

Three Month Visit
• assess effect of HRT on symptoms – the maximal benefit of HRT is usually seen within 3 months
• check bleeding pattern (see abnormal bleeding section)
• ask about side effects / compliance
• check blood pressure and weight
• reiterate information about breast awareness
• prescribe HRT for 6 months

Annual visits – unless there is an indication to review earlier
• check effectiveness of therapy
• check bleeding pattern (see abnormal bleeding section)
• ask about side effects / compliance
• review best type of therapy for patient e.g. consider change from sequential to continuous combined HRT
• take blood pressure
• reiterate breast awareness and need to continue with cervical screening
• discuss risks and benefits at the annual visit
• reassess risk factors

In women who continue to complain of menopausal symptoms:
• check adherence
• dose may be too low – increase dose or change from oral to non-oral route
• absorption may be poor e.g. bowel disorder – change from oral to non-oral route
• potential drug interaction – change from oral to non-oral route
• problems with patch adhesion or skin reaction - change to gel, smaller patch or oral preparation
• incorrect diagnosis of menopause e.g hypothyroidism or diabetes
• unrealistic patient expectations
• refer to specialist service

13. Duration of therapy

No arbitrary limits should be placed on the duration of HRT usage. However in the UK most women stop taking HRT within 2-3 years. The decision to continue or discontinue HRT should be made jointly by an informed woman with her healthcare professional.

Guidance from the Committee on Safety of Medicine says:
• use the lowest effective dose of HRT to control menopausal symptoms
• use HRT for the shortest length of time

Therefore it is important that the benefits and risks should be reassessed with each woman on an annual basis

13.1 Discontinuation

If a woman wishes to discontinue the dose can be reduced slowly over a 4-6 month period or stopped immediately. Gradual reduction may minimise the chance of symptom recurrence in the short term but makes no difference to symptoms in the longer term

If a woman taking a sequential HRT containing 2 mg estradiol valerate wants to slowly reduce the dose she can take a sequential HRT containing 1 mg estradiol valerate for 3 months, then take this preparation alternate days for 3 months (taking the estrogen tablets on alternate days
for the first two weeks of the cycle then the estrogen/progestogen tablets on alternate days for the next two weeks)

If menopausal symptoms persist or return, after counselling, prescribe a low dose HRT. Often this lower dose will control menopausal symptoms with fewer side-effects.

Remember HRT should be stopped immediately if any of the following occur:
- sudden severe chest pain (even if not radiating to left arm)
- sudden breathlessness (or cough with blood-stained sputum)
- unexplained swelling or severe pain in the calf of one leg
- severe stomach pain
- serious neurological effects, including an unusually severe, prolonged headache, especially if it is the first episode / getting progressively worse / sudden partial or complete loss of vision / sudden disturbance of hearing or other perceptual disorders / dysphasia / collapse / first unexplained epileptic seizure / motor disturbances / very marked numbness suddenly affecting one side or one part of body
- hepatitis, jaundice, or liver enlargement
- prolonged immobility after surgery or leg injury
- detection of a risk factor that contraindicates treatment

14. Risks of HRT

14.1 Breast Cancer

There appears to be no increased risk of breast cancer in users of ERT unlike women taking combined HRT where an increased risk becomes apparent about 5 years after starting therapy from the age of 50 years. This continues to increase with duration of use and reduces after stopping HRT. Five years after discontinuation this risk is the same as in women who have never used HRT.

The Women’s Health Initiative study reported an excess breast cancer risk of 1 per 1000 for combined HRT users each year, after 5 years of use, from the age of 50 years.

This increased risk is similar to:
- women who have experienced a late menopause (2.3% compared with 2.8% per year respectively)
- women who are obese
- those who have never had children
- those who drink two to three units of alcohol per day

This increased risk is not dependant on specific estrogens, progestogens, dosage, route of administration or regimen. The association between tibolone and breast cancer is not well established, however there appears to be a small increased risk above background. If breast cancer develops the prognosis tends to be better in women taking HRT than women developing sporadic cancers as these cancers are more likely to be oestrogen receptor positive. There is an increased recurrence rate of breast cancer in women prescribed combined HRT and tibolone.
In the absence of any breast symptoms, women do not need mammography prior to starting HRT and HRT users do not need more frequent breast screening

Women with an early menopause (before age 45) taking HRT:
- can be reassured that their risk of developing breast cancer is no greater than premenopausal women of a similar age

Women with a personal breast cancer history:
- have a small increased risk of breast cancer recurrence after 2-3 years use of a combined HRT and tibolone
- should discuss treatment options with a local menopause specialist or their Breast Multidisciplinary Team
- can be reassured that there is no evidence suggesting an increased risk of recurrence with vaginal estrogen preparations

Women with a close family history of breast cancer:
- may be at an increased risk of developing breast cancer but with no additional risk if HRT is used short term
- may require referral to the Family History clinic
- do not need mammography under 50 years unless it is recommended by the Family History clinic

Benign breast disease and HRT:
- HRT increases mammographic density which then diminishes on discontinuation
- increased mammographic density reduces the sensitivity of mammograms in detecting breast cancer
- there is no additional risk with HRT
- women with proliferative/atypical histological changes are at increased risk of breast cancer and specialist advice should be sought

14.2 Venous thromboembolism

Oral HRT and ERT increase the risk of VTE:
- with a small increased risk for oral ERT but approximately a 3 fold increased risk for oral combined HRT
- with the greatest risk is in the first year of HRT use
- with risk increasing with age, obesity, immobility, presence of a thrombophilia, personal or family history of VTE
- with the risk being dose dependent
- and is dependent on the route of administration. Non-oral administration avoids the 'first pass' effect on liver metabolism, decreasing VTE risk compared to oral HRT
- with an increased risk with certain progestogens such as nor-pregnane derivatives and medroxyprogesterone acetate
- accounting for 2 extra deaths per million users of HRT
- returning to background levels when HRT has been discontinued for 5 years
- with hospitalised users of HRT requiring appropriate thromboprophylaxis depending on their reason for admission and route of HRT administration.
Those using transdermal HRT do not need to stop their HRT prior to elective surgery.

Caution is required when prescribing for women:
- with a personal history of a VTE.
- who are obese. There is no national guideline advising an upper limit of BMI for HRT prescribing but many would not issue HRT to a woman with a BMI >40 kg/m².
- whose BMI is >30kg/m². Consider using a transdermal rather than oral preparation.
- with a strong/close family history of the disease (first line relative). Seek advice from a menopause specialist.
- with potential VTE risk factors. Low-dose, non-oral HRT (with micronized progesterone or dydrogesterone, if they have a uterus) is recommended.

14.3 Coronary Heart Disease (CHD)

Coronary heart disease:
- generally occurs at a later age in women than in men
- increases after the menopause

From current evidence:
- HRT should not be initiated or continued for primary or secondary prevention of cardiovascular disease
- there is no significant cardiovascular risk associated with HRT use in women aged 50-59
- the presence of cardiovascular risk factors does not contraindicate the use of HRT
- women over 60 starting HRT for menopausal symptom control should be advised of a possible excess cardiovascular risk and prescribed the lowest effective dose
- non-oral estradiol lowers LDL-cholesterol and triglycerides and may be a more suitable for women with risk factors for coronary heart disease
- there is no robust evidence on which to make a definitive statement for HRT management post-myocardial infarction. Patient management should be individualised and specialist advice sought.

14.4 Stroke

From current evidence:
- there is a very small risk of stroke in women taking oral HRT under the age of 60 years
- there is no increased risk of stroke with use of transdermal HRT
- any risk may be dose related therefore the lowest effective HRT dose should be used
- the background risk of stroke in women under the age of 60 is very low
- there is no robust evidence on which to make a definitive statement for HRT management post-stroke. Patient management should be
individualised and specialist advice sought.

14.5 Hypertension

Recent RCTs show that:
• HRT and ERT have no clinical effect on systolic and diastolic blood pressure

It is recommended that:
• women with controlled hypertension may take HRT
• hypertension should be controlled with anti-hypertensive medication
• blood pressure in hypertensive women should be monitored every 6 months or as indicated

14.6 Diabetes

Diabetics have a marked increased risk of myocardial infarction.
For diabetics taking HRT:
• there is little evidence of an additional myocardial infarction risk in those without cardiovascular disease
• conjugated equine estrogens raise HDL-cholesterol but also raise triglycerides
• HRT does not adversely affect glycaemic control
• non-oral estradiol lowers LDL-cholesterol and triglycerides and is the most suitable option for women with diabetes and those at risk of coronary heart disease
• micronised progesterone or dydrogesterone appear to have the least adverse effect on insulin sensitivity and HDL-cholesterol so is a good choice of progestogen for diabetics

14.7 Migraine

Migraine is very common:
• occurs in 7% of men and 19% of women
• may worsen in the peri-menopause and thought to be related to hormone fluctuations
• with its prevalence declining after the menopause

HRT in migraine sufferers:
• low dose, continuous combined HRT or tibolone may be helpful
• non-oral HRT such as patches or gels gives a steady hormone release and may improve migraine in some women
• changing or lowering the dose of estrogen or progestogen may help if migraine worsens

214.8 Dementia
Current evidence suggests that:
- neither HRT nor ERT improves symptoms in women with Alzheimer's disease
- there is little research investigating different preparations and duration effects
- HRT used early in the post-menopause may have a preventative effect

14.9 Ovarian Cancer

In women taking HRT:
- there may be a very small increased risk of ovarian cancer
- it may be acceptable as part of a supportive and symptomatic therapy for those with ovarian cancer
- there is no evidence that HRT use will adversely or favourably affect prognosis

14.10 Endometrial Cancer

The risk of endometrial cancer:
- is increased at least 4 fold in women with an intact uterus given unopposed ERT
- may be increased up to 2 fold in users of sequential HRT for five or more years
- is not increased in those taking continuous combined HRT

Following successful treatment for endometrial cancer (stages I and II):
- women can receive ERT
14.11 Summary of Risks of HRT

<table>
<thead>
<tr>
<th>Age range (years)</th>
<th>Time (years)</th>
<th>Background incidence per 1000 women years in Europe</th>
<th>Oestrogen only HRT – additional cases per 1000 HRT users</th>
<th>Oestrogen-progestogen HRT – additional cases per 1000 HRT users</th>
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15. Investigation of abnormal uterine bleeding

Those women with irregular vaginal bleeding taking HRT should be asked about:
- HRT compliance
- HRT absorption e.g. diarrhoea or vomiting
- any drug interactions e.g. liver enzyme inducing agents including St. John's Wort
- date of their last natural menstrual period because endogenous residual ovarian activity may lead to irregular bleeding in continuous combined HRT users

In the following situations further investigations are required and referral should be considered however, HRT does not needed to be stopped:
• heavy, prolonged or irregular bleeding in sequential HRT users
• bleeding associated with pain in sequential HRT users
• heavy bleeding after previous light bleeding in sequential HRT users
• if irregular bleeding persists for more than the first 6 months in long cycle users (2 quarterly cycles)
• continued vaginal bleeding after six months in users of continuous combined HRT
• if vaginal bleeding occurs after 6 months or more of amenorrhoea in users of continuous combined HRT

Immediate referral is advised in women with any of the above who are at increased risk of endometrial hyperplasia/endometrial carcinoma e.g. taking tamoxifen, those who are obese or diabetic.

A pelvic examination should be performed and consideration given to:
• performing a cervical sample, if indicated by the cervical screening programme
• performing a sexually transmitted infection screen, if appropriate

The method of investigation depends on local protocols and services but should include a transvaginal ultrasound and when indicated a hysteroscopy/endometrial biopsy.

16. Management of local urogenital problems

Safe treatment options:
• include local vaginal estrogen preparations which are best for the treatment of urogenital symptoms
• include estriol cream/pessaries, estradiol vaginal tablets and low-dose estradiol intravaginal rings
• acceptability is highest with low dose vaginal rings and estradiol vaginal tablets
• for the older woman and in those where topical application or pessary insertion may be difficult low dose estradiol vaginal rings are recommended
• additional progestogen is not required
• non-hormonal moisturisers and lubricants are suitable alternatives but are not on the local formulary and therefore should not be prescribed on FP10

A pelvic examination:
• should be performed in all women with urogenital symptoms prior to commencing local estrogen treatment

Local vaginal estrogen preparations:
• should be used nightly for the first 14 days then twice weekly thereafter
• are short acting preparations with symptoms returning on discontinuation
• may be necessary in those taking systemic HRT for the relief of urogenital symptoms
• have been linked with endometrial hyperplasia if used on a daily basis long
term
• given as low dose maintenance treatment (no more than twice weekly), do not raise estradiol levels above the postmenopausal range or increase endometrial thickness
• given as low dose maintenance treatment may be used long term but immediate investigation is advised if any vaginal bleeding occurs
• does not appear to cause adverse effects in women with a history of breast cancer or venous thromboembolism

17. Alternatives to HRT for controlling menopausal symptoms

These include lifestyle advice, herbal remedies, progestogens and non-hormonal preparations. None of these products are approved for use by the North of Tyne & Gateshead APC. There is limited evidence to suggest that complementary therapies improve menopausal symptoms but as women frequently ask their healthcare professional for advice it has been included in the guidance.

**Lifestyle advice**

The following lifestyle changes may be of benefit:

• regular exercise may reduce symptoms
• lighter clothing and sleeping in a cooler room may also help
• avoiding alcohol, spicy foods and stimulants such as caffeine may be of benefit
• stopping smoking
• losing weight if needed
• reducing stress/suggest relaxation techniques. CBT may be used alone or in combination with HRT to alleviate low mood and/or anxiety associated with the menopause.

**Bio-identical hormones**

Many women are asking about bio-identical hormone replacement therapy (BHRT) and are referring to the use of hormones that are identical on a molecular level with endogenous hormones.

Private providers are preparing unlicensed, custom-compounded products for women following saliva testing to measure their hormonal levels. These formulations, often skin creams, are purported to help a number of menopausal symptoms with very little scientific evidence to back the manufacturer’s claims.

Most menopause specialists prefer to discuss ‘body identical’ HRT which includes licensed non-oral estradiol in the form of patches and gels along with oral micronised progesterone.

**Botanicals or herbal remedies**

There is no strong evidence that any botanicals or herbal remedies help menopausal symptoms and some can do positive harm. Preparations vary with regard to their quality and
Dietary phytoestrogens:

- are found in soy products, red clover (40-80mg daily), oil seeds and probably other legumes
- no long-term safety data is available and there is conflicting evidence about whether they have any effect on vasomotor symptoms
- should be avoided during pregnancy, lactation, anyone with hormone-dependant tumours and those with a contraindication to estrogens
- red clover and dong quai extracts contain coumarins and may adversely affect those with bleeding disorders or taking anticoagulants

Black Cohosh (8mg daily):

- may relieve vasomotor symptoms however the content of preparations vary and the safety of Black Cohosh is uncertain
- has an MHRA warning [http://www.mhra.gov.uk/NewsCentre/Pressreleases/CON199545](http://www.mhra.gov.uk/NewsCentre/Pressreleases/CON199545)
- may cause potential liver damage
- may produce side effects including gastrointestinal complaints, hypotension, headache, dizziness, nausea and allergic reactions
- may interact with conventional antihypertensive drugs and overdosing can produce toxicity

Many other complementary and alternative therapies are advocated for the treatment of menopausal symptoms but there is no evidence that the following have any effect:

- wild yam cream
- dong quai
- agnus castus (chasteberry)
- liquorice root
- valerian root
- ginko biloba
- ginseng
- vitamin E
- evening primrose oil
- sage

**Progestogen-only alternatives**

Progestogens:

- may help vasomotor symptoms but its use is off-label
- Medroxyprogesterone acetate 10mg daily may reduce vasomotor symptoms by 60% but there is no long term safety data for women with a personal history of breast cancer or VTE

Progesterone transdermal creams:

- have little effect on vasomotor symptoms
- produce systemic levels that are inadequate to provide endometrial protection with estrogen
- produce no beneficial effect on bone density
- have not been studied in women with a personal history of breast cancer

**Non-hormonal alternatives**

Clonidine 75 microgram twice daily:
- is not approved by the NoT&G APC for this indication
- licensed to reduce vasomotor symptoms but generally ineffective
- decreases hot flushes in women on tamoxifen
- produces marginal benefits over placebo in post-menopausal women
- dose should be increased slowly and follow up arranged
- gives troublesome side-effects for some women such as dry mouth, constipation, drowsiness and dizziness
- may interact with antihypertensives

Certain antidepressants have been shown to help vasomotor symptoms but their use is ‘off-label’:
- SSRIs and SNRIs may be effective in reducing hot flushes
- Fluoxetine (20mg) reduces hot flushes by 60%
- Venlafaxine (37.5mg, 75mg or 150mg) has been shown to reduce hot flushes by 37%, 61% and 61% compared to 27% reduction for placebo. Usual starting dose is 37.5mg daily with gradual increase to reduce side effects such as nausea, dry mouth, insomnia, agitation and confusion.
- symptoms should respond within 2 weeks of commencing treatment
- there are no long term studies to show that a reduction in vasomotor symptoms is maintained
- there is no evidence that SSRI or SNRIs alleviate low mood in menopausal women in the absence of a diagnosis of depression

SSRI, SNRI and clonidine should not be routinely used first line for the management of vasomotor symptoms, unless there are contraindications to hormonal replacement. SSRIs paroxetine and fluoxetine **should not be used** in women taking tamoxifen.

Gabapentin 900mg daily:
- has been shown against placebo to reduce hot flushes by 42-73%
- its use is ‘off-label’
- adverse effects include drowsiness, arthralgia, weight increase, unsteadiness and dizziness side-effects may be reduced by gradual increase in dose

**18. Osteoporosis**

Osteoporosis is characterised by compromised bone strength that predisposes to an increased risk of fracture, particularly at the spine, hip and forearm. It is defined by a T score of -2.5 or below on dual energy x-ray absorptiometry (DXA) scanning.

For women with premature menopause HRT is recommended until the age of natural menopause as an osteoporosis preventive measure.
Fragility fracture risk assessment

Before considering commencing preventative treatment a fragility fracture risk assessment must be undertaken.

For women aged 50 to 64 consider undertaking an assessment in the presence of the following risk factors:

- previous fragility fracture
- current use or frequent recent use of oral or systemic glucocorticoids
- history of falls
- family history of hip fracture
- other causes of secondary osteoporosis
- low body mass index (BMI) (less than 18.5 kg/m²)
- smoking
- alcohol intake of more than 14 units per week for women

Fracture Risk is estimated using either FRAX (with or without BMD) or QFracture, to estimate the 10-year predicted absolute fracture risk (NICE guidance CG146).

http://www.shef.ac.uk/FRAX/
http://www.qfracture.org/
http://www.nice.org.uk/guidance/cg146

Do not routinely measure BMD to assess fracture risk without prior assessment using FRAX (without a BMD value) or QFracture.

The NICE guidance (CG146) advises that following risk assessment with FRAX or QFracture, consider measuring BMD with DXA scanning in people whose fracture risk is in the region of an intervention threshold for a proposed treatment, and recalculate absolute risk using FRAX with the BMD value. As a standardised threshold has not yet been set a practical approach is to utilise the North of Tyne Osteoporosis guideline.


Assessment of dietary intake should occur and calcium and vitamin D3 supplementation provided unless clinicians are confident that women who receive treatment for osteoporosis have an adequate intake of calcium and are vitamin D replete. Calcium and vitamin D may be the most appropriate treatment for frail elderly women. The doses used should be 1-1.2g/day of calcium and 800-1000 IU/day of colecalciferol.

Primary prevention of osteoporotic fragility fracture in post-menopausal women (NICE TA160)

HRT has been shown to be useful in the prevention and treatment of osteoporosis in menopausal women under the age of 60. Other drugs are preferentially used for the prevention of osteoporotic fragility fractures in postmenopausal women if this is the sole indication for commencing HRT.

http://www.nice.org.uk/guidance/ta160
The bone protective effects of estrogen are dose dependent. The effect declines after discontinuation of HRT.

Alendronate (70mg) is the first line NICE recommended treatment option. It is recommended for postmenopausal women younger than 65 years who have an independent clinical risk factor for fracture (parental history of hip fracture, alcohol intake of 4 or more units per day, and rheumatoid arthritis) and at least one additional indicator of low BMD (low body mass index (defined as less than 22 kg/m²), medical conditions such as ankylosing spondylitis, Crohn's disease, conditions that result in prolonged immobility, and untreated premature menopause) and who are confirmed to have osteoporosis (that is, a T-score of -2.5 SD or below).

There is increasing awareness of the potential for adverse effects with long term therapy with Alendronate, notably predisposing to femoral shaft fragility fractures due to prolonged suppression of bone turnover, therefore the practice of a drug holiday after five years is common.

Etidronate, Risedronate and Denosumab can be considered alternatives to alendronate in certain circumstances (see NICE guidance TA160 for further details).

Secondary prevention of osteoporosis in post-menopausal women (NICE TA161)

Secondary prevention is required for those who have osteoporosis and have sustained a clinically apparent osteoporotic fracture. Patients with a suspected fracture need DEXA scan and treatment. Advice should have been offered by fracture liaison service locally, if not, individuals should be referred into this service. Locally, the initial recommended treatment is alendronate, as suggested by the NICE guideline, as it is the most cost-effective treatment at the present time.

http://www.nice.org.uk/guidance/ta161

Risedronate, Etidronate, Raloxifene and Denosumab may be considered as an alternative where issues of tolerance or contraindications occur or in specific circumstances (see NICE guidance for details)
### Appendix 1 Useful contacts

#### National

National Osteoporosis Society  
Camerton  
Bath  
BA2 0PJ  

Helpline 0808 800 0035  
[www.nos.org.uk](http://www.nos.org.uk)

#### Local

New Croft Centre  
Market Street (East)  
Newcastle upon Tyne  
NE1 6ND  

0191 229 2862  

#### National

Women's Health Concern Ltd  
Spracklen House, East Wing  
Dukes Place  
Marlow  
BUCKINGHAMSHIRE  
SL7 2QH  

Office: 01628 890199  

#### Local

Musculo Skeletal Unit  
Freeman Hospital  
High Heaton  
NEWCASTLE UPON TYNE  
NE7 7DN  

Tel: 0191 233 6161  

#### National

The British Menopause Society  
Spracklen House, East Wing  
Dukes Place  
Marlow  
BUCKINGHAMSHIRE  
SL7 2QH  

Tel: 01628 890199  
[www.the-bms.org/](http://www.the-bms.org/)

#### Local

Menopause Matters  
Skewbridge, Mouswald, Dumfries DG1 4LY  
[http://www.menopausematters.co.uk/](http://www.menopausematters.co.uk/)

FPA (Family Planning Association)  
23-28 Penn Street  
London N1 5DL  
## Appendix 2

### Suggested reading

<table>
<thead>
<tr>
<th>Source</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>Faculty of Sexual and Reproductive Healthcare Guideline</td>
<td>Contraception for women aged over 40 years</td>
</tr>
<tr>
<td>National Institute for Health and Care Excellence</td>
<td>NG 23 Menopause: clinical guideline</td>
</tr>
<tr>
<td>National Institute for Health and Care Excellence</td>
<td>CG 146 Osteoporosis: assessing the risk of fragility fracture (2012)</td>
</tr>
<tr>
<td>National Institute for Health and Care Excellence</td>
<td>TA160 Osteoporosis - primary prevention (2011)</td>
</tr>
<tr>
<td>National Institute for Health and Care Excellence</td>
<td>TA161 Osteoporosis - secondary prevention including strontium ranelate (2011)</td>
</tr>
</tbody>
</table>

### Recommended websites:

- [www.frsh.org](http://www.frsh.org)
- [www.nice.org.uk](http://www.nice.org.uk)
- [www.thebms.org.uk](http://www.thebms.org.uk)
- [www.shef.ac.uk/FRAX](http://www.shef.ac.uk/FRAX)
- [http://www.qfracture.org](http://www.qfracture.org)