

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

SCOPE

1 Guideline title

Menopause: diagnosis and management of menopause

1.1 *Short title*

Menopause

2 The remit

The Department of Health has asked NICE: 'to produce a clinical guideline on the diagnosis and management of menopause'.

3 Clinical need for the guideline

3.1 *Epidemiology*

- a) Menopause is a biological stage in a woman's life. It occurs when a woman stops menstruating, and it marks the end of her natural reproductive life. The changes associated with menopause occur when the ovaries begin to stop functioning. This includes the cessation of egg (oocyte) maturation and of oestrogen and progesterone secretion.
- b) A woman has a finite number of oocytes at birth, which declines with each menstrual cycle. The menopause is characterised by the eventual depletion of a woman's oocyte store and cessation of menstruation. Menstrual cycle irregularity often occurs before periods stop completely.
- c) Most tissues contain oestrogen receptors through which the hormone exerts its effects. The most immediate changes of

reduced oestrogen levels are evident in the regulation of the menstrual cycle. However, oestrogen depletion associated with the menopause has many other effects on the body – for example, vasomotor, musculoskeletal, uro-genital and psychosocial symptoms. It has also been shown to have an impact on the function of other systems in later life, including bone and the cardiovascular system. Oestrogen depletion explains some of the gender differences in the rates of osteoporosis.

- d) Perimenopause, also called the menopausal transition, is the interval in which a woman's body makes a natural shift from regular cycles of ovulation and menstruation during the reproductive years towards the menopause.
- e) A woman is defined as postmenopausal from 1 year after her last period. Within the UK population, the mean age of the natural menopause is 51 years. However, cross-cultural studies have shown that the age of menopause varies by ethnicity.
- f) Premature ovarian insufficiency (also known as premature ovarian failure or premature menopause) is usually defined as menopause before the age of 40 years. It can occur naturally or iatrogenically (the result of treatment). Premature ovarian insufficiency and early perimenopause are associated with an increased risk of mortality, and serious morbidity including cardiovascular and neurological disease, psychiatric disorders and osteoporosis. Lower socioeconomic status has been associated with premature ovarian insufficiency.
- g) Many of the associated symptoms of menopause are short lived and lessen or disappear over time. The most common symptoms include vasomotor symptoms (for example hot flushes and sweats), mood symptoms (for example low mood) and urinary symptoms (for example urge incontinence). Overall, 84% of women experience one or more of the classic menopausal symptoms.

About 70% of women have vasomotor symptoms, and in most cases the symptoms are short-lived. However, in 25% of women these symptoms cause significant morbidity and in 10% of symptomatic women, symptoms can last for up to 15 years.

- h) Postmenopausal women are at increased risk of a number of long-term conditions, such as osteoporosis, cardiovascular disease, and changes in the vagina and bladder.
- i) Climacteric is defined as the syndrome of endocrine (hormonal), somatic (bodily), and psychological changes (mood) experienced by women at menopause.
- j) There are 13 million women over 45 years in the UK. This number has been steadily increasing and is forecast to continue to rise. The subsequent increase in women going through the menopause is expected to result in more new referrals to secondary care from women requiring short-term symptom control, and who have associated long-term health issues.

3.2 Current practice

- a) The Women's health initiative (published using USA data in 1991) and the Million women study (published using UK data in 2007) highlighted the disparity of treatment for menopausal symptoms. Within those studies it was reported that menopause-related GP consultations for women aged 45–64 years decreased from 18% in 1996 to 10% in 2005 (for women consulting at least once). Furthermore, more than 60% of women manage their menopausal symptoms without any contact with healthcare professionals, often through social support and obtaining advice from friends, family and the internet.
- b) Variations in consultation patterns for menopausal symptoms depend on many factors, including cultural, educational and psychosocial. However, it is currently thought that more than one-

third of all women want more support about menopausal symptoms from their GP or practice nurse.

- c) The information and support offered to women during and following the menopause is thought to be variable and, for some, inadequate. A UK-based survey published in 2007 indicated that most women would welcome more information about the menopause. To improve the information provided, and to facilitate women being able to make an informed choice, some professional groups have suggested that all women should be invited for a health and lifestyle consultation on their 50th birthday which would include a discussion of menopause symptoms and long-term sequelae of oestrogen depletion.
- d) Treatments indicated for menopause-related symptoms include lifestyle advice, hormone replacement therapy (HRT), herbal remedies, complementary (alternative) therapies and antidepressants. In the 2007 UK-based survey, nearly three-quarters of women reported they did not know enough about HRT to make informed choices, 85% felt they did not know enough to make informed choices regarding alternative therapies for menopause-related symptoms and 95% would try alternative therapies before HRT in the belief that they were more 'natural'.
- e) In the UK, the HRT prescription rate by GPs fell from 6.9% in 1996 to 2.6% in 2005, although rates of referral to specialist care (gynaecology), although uncommon, increased from 0.1% to 1.1% over the same interval.
- f) There is published evidence that physician speciality is significantly associated with HRT use. For example, in the USA women receiving care from gynaecologists are 2.6 times more likely to use HRT than that women receiving care from family physicians.
- g) The use of HRT in the UK is strongly linked to socioeconomic status, with women from lower socioeconomic status being less

likely to use HRT. Inequalities in referral rates have also been associated with socioeconomic status, geography and age.

- h) The long-term benefits and risks of HRT are not fully agreed. The Women's Health Initiative study found that HRT prevents osteoporotic fractures, but subsequent research has suggested there is an association between prolonged HRT use and increased rates of breast cancer and cardiovascular disease. However, the association between HRT and cardiovascular disease has subsequently been disputed.
- i) In summary, a large number of women in the UK experience symptoms of the menopause which in many cases can severely affect their quality of life (both in the short and long term). Not all of these women seek treatment, and in those that do the provision help especially in primary care appears to be variable and often inappropriate.

4 The guideline

The guideline development process is described in detail on the NICE website (see section 6, 'Further information').

This scope defines what the guideline will (and will not) examine, and what the guideline developers will consider. The scope is based on the referral from the Department of Health.

The areas that will be addressed by the guideline are described in the following sections.

4.1 Population

4.1.1 Groups that will be covered

- a) Menopausal women (covering the perimenopause and post-menopause).

- b) Women with premature ovarian insufficiency (irrespective of cause).

4.1.2 Groups that will not be covered

- a) Women who are pregnant.
- b) Women who are breastfeeding.
- c) Women and young people under 18 years.
- d) Men.
- e) Transgender women.

4.2 *Healthcare setting*

- a) All settings in which NHS care is received or commissioned (including primary care).

4.3 *Clinical management*

4.3.1 Key clinical issues that will be covered

- a) Diagnosis and classification of the stages of menopause.
- b) Optimal clinical management of menopause-related symptoms, including:
 - treatments for symptomatic relief (specifically vasomotor, musculoskeletal, urogenital and psychosocial symptoms, and altered sexual function) including:
 - hormonal pharmaceutical treatments:
 - ◇ oestrogen alone (oral, transdermal or vaginal)
 - ◇ oestrogen combined with progestogen
 - ◇ testosterone
 - ◇ tibolone
 - ◇ bio-identical hormones
 - ◇ selective oestrogen-receptor modulators

- non-hormonal pharmaceutical treatments:
 - ◇ selective serotonin reuptake inhibitors
 - ◇ serotonin–noradrenaline reuptake inhibitors
 - ◇ gabapentin
 - ◇ clonidine
- non-pharmaceutical treatment:
 - ◇ phytoestrogen/soy-containing products
 - ◇ herbal preparations (including black cohosh/red clover)
 - ◇ acupuncture
 - ◇ lifestyle advice
- psychological therapies
 - ◇ cognitive behavioural therapy

- risks and benefits of treatment
- timing of treatment
- monitoring treatment
- duration of treatment
- treatment withdrawal strategies.

Note that guideline recommendations will normally fall within licensed indications exceptionally, and only if clearly supported by evidence, use outside a licensed indication may be recommended. The guideline will assume that prescribers will use a drug's summary of product characteristics to inform decisions made with individual patients.

- c) Contribution of HRT to prevent long-term sequelae of menopause (especially osteoporosis and cardiovascular disease).
- d) Diagnosis and management of premature ovarian insufficiency.

4.3.2 Clinical issues that will not be covered

- a) Contribution of all other agents (excluding HRT) in preventing long-term sequelae of menopause (especially osteoporosis and cardiovascular disease).
- b) Hormonal treatment in women at risk of hereditary or familial breast cancer or are undergoing treatment for breast cancer or have previously had breast cancer.
- c) Treatment of long-term sequelae of oestrogen depletion caused by menopause (especially osteoporosis and cardiovascular disease).
- d) Premenopausal prevention of menopause-related symptoms (specifically vasomotor, musculoskeletal, urogenital, psychosocial symptoms and altered sexual function).
- e) Investigation of the cause of premature ovarian insufficiency.
- f) Contraception during the menopause.

4.4 Main outcomes

4.4.1 Short-term outcomes (up-to 5 years)

- a) Change in menopausal symptom scores that derive numerical results from a combination of menopausal symptoms (for example the Greene Climacteric Scale [GCS]).
- b) Reduction in frequency (or intensity) of:
 - vasomotor symptoms
 - musculoskeletal symptoms
 - urogenital symptoms
 - psychosocial symptoms
 - sexual function disturbance.

- c) Treatment-related adverse effects.
- d) Health-related quality of life.

4.4.2 Long-term outcomes

- a) Mortality.
- b) Coronary events (myocardial infarction or coronary death).
- c) Stroke (ischaemic or haemorrhagic) or transient ischaemic attack.
- d) Venous thromboembolism (pulmonary embolism or deep vein thrombosis).
- e) Breast cancer.
- f) Colorectal cancer.
- g) Lung cancer.
- h) Endometrial cancer.
- i) Ovarian cancer.
- j) Gall bladder disease.
- k) Osteoporotic fractures (hip and wrist fractures, clinically diagnosed vertebral fractures, total clinically diagnosed fractures).
- l) Cognitive function and dementia (including Alzheimer's disease).
- m) Metabolic syndrome.
- n) Health-related quality of life.

4.5 Review questions

Review questions guide a systematic review of the literature. They address only the key clinical issues covered in the scope, and usually relate to interventions, diagnosis, prognosis, service delivery or patient experience.

Please note that these review questions are draft versions and will be finalised with the Guideline Development Group.

4.5.1 Diagnosis and classification of the stage of menopause

- a) What is the accuracy of the following in the diagnosis of peri-menopause and menopause:
- menstrual cycle regularity
 - symptoms (especially hot flushes, sweats, shivering, palpitations, low mood, sleep disturbances, urinary incontinence, vulvo–vaginal dryness and/or reduced libido)
 - endocrine changes (specifically follicle-stimulating hormone, anti-Müllerian hormone, oestrogen or inhibin B) and total antral follicle count?
- b) What is the effectiveness of classification systems (for example STRAW +10) compared with non-structured classification systems in the diagnosis of the menopause?

4.5.2 Optimal clinical management of short-term (up to 5 years) menopause-related symptoms

- c) What is the comparative effectiveness (including risks and benefits) of different therapies compared with placebo and each other for the relief of individual acute menopause-related symptoms (specifically vasomotor, urogenital, psychosocial, musculoskeletal symptoms and altered sexual function) including:
- hormonal pharmaceutical treatments:
 - oestrogen alone (oral, transdermal or vaginal)
 - oestrogen combined with progestogen
 - testosterone
 - tibolone
 - bio-identical hormones

- selective oestrogen-receptor modulators
 - non-hormonal pharmaceutical treatments:
 - selective serotonin reuptake inhibitors
 - serotonin–noradrenaline reuptake inhibitors
 - gabapentin
 - clonidine
 - non-pharmaceutical treatment:
 - phytoestrogen/soy-containing products
 - herbal preparations (including black cohosh/red clover)
 - acupuncture
 - lifestyle advice
 - psychological therapies
 - cognitive behavioural therapy?
- d) At what intervals should clinical review be undertaken to assess the effectiveness and safety of effective treatments and to determine when patients need to be referred to secondary care?

If HRT is found to be effective in 4.5.2.c, the following question will be addressed:

- e) In perimenopausal and postmenopausal women using HRT for symptom relief, what is the effectiveness of an abrupt HRT discontinuation strategy compared with a tapered HRT discontinuation strategy?

4.5.3 Recognition and amelioration of the long-term sequelae of oestrogen depletion caused by menopause – specifically urogenital atrophy, osteoporosis and cardiovascular disease

- f) What is the long-term effectiveness of local oestrogens for the treatment of urogenital atrophy?

- g) What is the effectiveness of HRT compared with placebo on the subsequent development of cardiovascular disease in women at different stages of the menopause?
- h) What is the incidence of osteoporosis in:
- postmenopausal women who have used short-term HRT
 - postmenopausal women who have used long-term HRT
 - postmenopausal women who have not used HRT?
- i) What is the effect of HRT administered for menopausal symptoms on the subsequent incidence of breast cancer, venous thromboembolism, sarcopenia and type 2 diabetes?

4.5.4 Diagnosis and management of premature ovarian insufficiency

- j) What is the accuracy of the following in the diagnosis of premature ovarian insufficiency in women under 40 years with up to 12 months amenorrhoea:
- menstrual cycle regularity
 - symptoms (especially hot flushes, sweats, shivering, palpitations, low mood, sleep disturbances, urinary incontinence, vulvo–vaginal dryness and/or reduced libido)
 - endocrine changes (specifically follicle-stimulating hormone, anti-Müllerian hormone, oestrogen or inhibin B) and total antral follicle count?
- k) What is the effectiveness of HRT compared with combined oral contraceptives for the management of premature ovarian insufficiency?

4.6 Economic aspects

Developers will take into account both clinical and cost effectiveness when making recommendations involving a choice between alternative interventions. A review of the economic evidence will be conducted and

analyses will be carried out as appropriate. The preferred unit of effectiveness is the quality-adjusted life year (QALY), and the costs considered will usually be only from an NHS and personal social services (PSS) perspective.

Further detail on the methods can be found in 'The guidelines manual' (see 'Further information').

4.7 Status

4.7.1 Scope

This is the consultation draft of the scope. The consultation dates are 24 May 2013 to 21 June 2013.

4.7.2 Timing

The development of the guideline recommendations will begin in August 2013.

5 Related NICE guidance

5.1 Published guidance

5.1.1 Other related NICE guidance

- [Fertility](#). NICE clinical guideline 156 (2013).
- [Osteoporosis](#). NICE clinical guideline 146 (2012).
- [Epilepsy](#). NICE clinical guideline 137 (2012).
- [Patient experience in adult NHS services](#). NICE clinical guideline 138 (2011).
- [Alendronate, etidronate, risedronate, raloxifene, strontium ranelate and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women \(amended\)](#). NICE technology appraisal 161 (2011).
- [Alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women \(amended\)](#). NICE technology appraisal 160 (2011).
- [Chronic heart failure](#). NICE clinical guideline 108 (2010).
- [Depression in adults](#). NICE clinical guideline 90 (2009).

- [Early and locally advanced breast cancer](#). NICE clinical guideline 80 (2009).
- [Heavy menstrual bleeding](#). NICE clinical guideline 44 (2007).
- [Familiar breast cancer](#). NICE clinical guideline 41 (2006).
- [Statins for the prevention of cardiovascular events](#). NICE technology appraisal 94 (2006).

5.2 Guidance under development

NICE is currently developing the following related guidance (details available from the NICE website):

- [Familial breast cancer \(update\)](#). NICE clinical guideline. Publication expected June 2013.
- [Urinary incontinence](#). NICE clinical guideline. Publication expected July 2013.
- [Lipid modification \(update\)](#). NICE clinical guideline. Publication expected July 2014.

6 Further information

Information on the guideline development process is provided in the following documents, available from the NICE website:

- [‘How NICE clinical guidelines are developed: an overview for stakeholders the public and the NHS’](#)
- [‘The guidelines manual’](#).

Information on the progress of the guideline will also be available from the [NICE website](#).