NICE National Institute for Health and Care Excellence

2019 surveillance of menopause: diagnosis and management (NICE guideline NG23)

Surveillance report

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Surveillance decision

We will update the NICE guideline on menopause.

The update will cover managing urogenital atrophy and the long-term benefits and risks of hormone replacement therapy (HRT).

Reasons for the decision

We initially consulted on the proposal to not update the guideline. At that time, the identified new evidence was broadly in line with the guideline or showed inconsistent effects across studies so there was no clear indicator for proposing an update.

We also identified new evidence on treating vulvar and vaginal atrophy. Ospemifene is licensed in the UK for treating moderate to severe symptomatic vulvar and vaginal atrophy in women who are not candidates for vaginal oestrogen. Prasterone is licensed in the UK for treating vulvar and vaginal atrophy in postmenopausal women having moderate to severe symptoms.

The cost of prasterone is comparable with available intravaginal oestrogen pessaries, and although ospemifene is more expensive, its use is restricted to a smaller group of women for whom intravaginal oestrogen is not suitable. Therefore, we did not expect these treatments to have a substantial impact on NHS resources. This led to our initial proposal to not update this section of the guideline.

During consultation, a new study on the risk of breast cancer associated with HRT was published, accompanied by a Medicines and Healthcare products Regulatory Agency (MHRA) Drug Safety Update based on the results of the study. This was the main reason for changing the conclusion to recommend an update to the guideline.

This new study performed detailed and complex analyses. The results cannot be easily compared directly with the risk data considered when developing the guideline. The new study data on risk of breast cancer was reported over different treatment and follow-up periods than are detailed currently in the guideline.

For up to 5 years' use of HRT and follow up of 5 years to 10 years, the risks of breast

cancer reported in the new study were similar to those detailed in the guideline. However, the MHRA Drug Safety Update highlighted that 'some excess risk of breast cancer with systemic HRT persists for more than 10 years after stopping; the total increased risk of breast cancer associated with HRT is therefore higher than previous estimates'. The MHRA Drug Safety Update, based on the results of the new study, therefore suggests that risk data in the guideline, particularly for people who have stopped taking HRT, are out of date and an update is necessary.

However, the new study conducted a case-control analysis of individual participant data from 568,859 women. The review protocols from the guideline excluded this study design. Many of the studies informing the paper were excluded from the guideline. Similarly, many of the studies informing the guideline were excluded from the paper dataset. Additionally, in surveillance we identified 10 new cohort studies that measured the effects of HRT on breast cancer, only 1 of which was included in the new study. Notably, 1 analysis of more than 1 million women (Brusselaers et al. 2018) was not included in the new study.

Across all identified studies there are inconsistencies in the direction and size of effects of different types and durations of HRT on rates of breast cancer. For example, the size of the effects of HRT on breast cancer reported in Brusselaers et al. 2018 (more than 1 million women) were consistently smaller than the effects reported in the new study (more than half a million women).

Therefore, we will update the section of the guideline on the long-term risks and benefits of HRT. While the update is in process, we will remove the risk table for breast cancer and cross-refer to the MHRA risk table until the update publishes.

However, if the update process results in the inclusion of case-control studies for breast cancer, then all other risks and benefits of HRT should be reconsidered using the same revised methods.

Additionally, we decided that the section on urogenital atrophy should be updated to include ospemifene and prasterone. Stakeholder feedback indicated a desire for these drugs to be considered in an update and changes in the benefits and risk profiling of HRT may lead to changes in acceptability of HRT to women and therefore increase the prominence of other interventions for treatment of menopausal symptoms.

Other sections of the guideline

New evidence for other treatments for short-term menopausal symptoms was identified, including drug treatments, psychological treatments, and alternative medicine and complementary therapies. However, the evidence for these treatments did not indicate a need to update the guideline at this time because each intervention was usually assessed in a single small trial, which was deemed insufficient to change existing recommendations.

We identified 1 study for each of the sections on diagnosing perimenopause and menopause and diagnosing and managing premature ovarian insufficiency, but neither study indicated an update was necessary.

For further details and a summary of all evidence identified in surveillance, see appendix A.

Overview of 2019 surveillance methods

NICE's surveillance team checked whether recommendations in menopause (NICE guideline NG23) remain up to date.

The surveillance process consisted of:

- Feedback from topic experts via a questionnaire.
- A search for new or updated Cochrane reviews.
- Examining related NICE guidance and quality standards and NIHR signals.
- A search for ongoing research.
- Examining the NICE event tracker for relevant ongoing and published events.
- Literature searches to identify relevant evidence.
- Assessing the new evidence against current recommendations to determine whether or not to update sections of the guideline, or the whole guideline.
- Consulting on the proposal with stakeholders.
- Considering comments received during consultation and making any necessary changes to the proposal.

For further details about the process and the possible update decisions that are available, see ensuring that published guidelines are current and accurate in developing NICE guidelines: the manual.

Evidence considered in surveillance

Search and selection strategy

We searched for new evidence related to the whole guideline.

We found 123 studies in a search for randomised controlled trials (RCTs), Cochrane reviews and observational studies published between 13 January 2015 and 7 May 2019.

We also included 5 relevant studies from a total of 12 identified by topic experts, all of which were also identified by the searches.

We added 3 relevant studies suggested by stakeholders.

From all sources, we considered 131 studies to be relevant to the guideline.

See appendix A for details of all evidence considered, and references.

Selecting relevant studies

We included RCTs that had at least 100 participants because of a large volume of small studies.

Ongoing research

We checked for relevant ongoing research; of the ongoing studies identified, 2 studies were assessed as having the potential to change recommendations. Therefore, we plan to check the publication status regularly and evaluate the impact of the results on current recommendations as quickly as possible. These studies are:

- Effect of menopause relief EP-40 in women with menopausal symptoms – This RCT is assessing complementary therapies, including 2 doses of standardised black cohosh. The NICE guideline currently notes that 'there is some evidence that isoflavones or black cohosh may relieve vasomotor symptoms' but that 'multiple preparations are available and their safety is uncertain, different preparations may vary and interactions with other medicines have been reported'. This ongoing study may provide further evidence in this area.
- Can nurse delivered cognitive behavioural therapy reduce the impact of hot flushes and night sweats in women who have had breast cancer? – This RCT is assessing the effects of cognitive behavioural therapy on vasomotor symptoms of menopause.

Intelligence gathered during surveillance

Views of topic experts

We considered the views of topic experts who were recruited to the NICE Centre for Guidelines Expert Advisers Panel to represent their specialty. For this surveillance review, topic experts completed a questionnaire about developments in evidence, policy and services related to the guideline.

We sent questionnaires to 13 topic experts and received 7 responses. The topic experts who provided feedback were: GPs with a special interest in gynaecology and women's health, nurse consultants in gynaecology, consultant gynaecologist, academic clinical psychologist, and a consultant medical oncologist with a special interest in breast cancer.

Overall, 3 topic experts thought that the guideline should be updated and 4 thought that an update was not necessary. The issues that topic experts thought could be addressed in an update were:

- Expanding on recommendations for women with breast cancer (and other hormone-dependent cancers), for example how treatments for vaginal atrophy might differ for women on tamoxifen and those on aromatase inhibitors. There is some overlap across NICE guidelines, particularly in the NICE guidelines on early and locally advanced breast cancer and familial breast cancer. The NICE guideline on menopause already has cross references to the breast cancer guidelines. These guidelines have more detailed recommendations for women with or at risk of breast cancer who have treatment-related menopausal symptoms. We did not find sufficient new evidence to support an update of the menopause guideline in this area.
- Alternative and complementary therapies were highlighted, but new evidence did not confirm a clear need to update this area. We found 1 ongoing study of black cohosh that may provide further evidence in this area; we will regularly check for publication of results from this study.

- Psychological therapies for vasomotor symptoms and depression, but new evidence did not confirm a clear need to update in these areas. Postmenopausal women meeting criteria for generalised anxiety or depression should receive treatment according to the relevant NICE guidelines. We found an ongoing study of cognitive behavioural therapy for managing hot flushes and night sweats in women who have had breast cancer; we will regularly check for publication of results from this study.
- Topic experts had conflicting views on the rate of uptake of the guideline in their local services; however, we did not identify any additional information that would allow us to explore this issue further.

Views of stakeholders

Stakeholders are consulted on all surveillance reviews except if the whole guideline will be updated and replaced. Because the original surveillance proposal was to not update the guideline, we consulted with stakeholders.

Overall, 10 stakeholders commented, 9 of whom disagreed with the decision not to update the guideline. This included 5 professional bodies, 2 pharmaceutical companies, 1 patient organisation and 1 NHS Trust. The stakeholder that agreed with the decision not to update the guideline was a patient organisation.

Stakeholders' comments suggested that an update should look at the risks and benefits of hormone replacement therapy (HRT; including effects on cardiovascular disease and breast cancer), effects of testosterone, treatment of premature ovarian insufficiency, terminology around compounded bioidentical hormones, low mood during menopause and new treatments for urogenital atrophy including ospemifene, prasterone and laser treatment. After reviewing the comments, very few of the additional references provided by stakeholders to support their suggestions met the criteria for inclusion, mostly because the design of the studies did not match the evidence reviews for the guideline. Three studies were added as a result of stakeholder consultation, but the findings were generally consistent with current recommendations.

However, stakeholders' comments on the importance of evidence on treatments for urogenital atrophy and the newly published evidence and Medicines and Healthcare products Regulatory Agency (MHRA) safety advice on risks of breast cancer after HRT use identified in surveillance, influenced the change from a proposal not to update the guideline to a decision to update it.

See appendix B for full details of stakeholders' comments and our responses.

See ensuring that published guidelines are current and accurate in developing NICE guidelines: the manual for more details on our consultation processes.

Equalities

Several stakeholders highlighted equalities issues in their consultation comments. However, these issues often did not involve groups with protected characteristics.

One stakeholder noted that the guideline has no recommendations for people with learning disabilities; however the NICE guideline on care and support of people growing older with learning disabilities recommends discussing with people the changes that may occur with age and asking them about and monitoring them for symptoms of common age-related conditions or changes in any existing conditions, including menopause. Therefore, we concluded that an update to address this area was not necessary.

This stakeholder also suggested that an updated guideline should cover transgender issues and HRT; however, it was unclear whether that meant specific hormonal needs for transgender people or people being treated fairly within NHS services. We expect services to follow recommendations on individualised care, irrespective of gender identity.

Overall, we did not identify any equalities issues that would need to be considered in an update of the guideline.

Overall decision

After considering all evidence and other intelligence and the impact on current recommendations, we decided that an update is necessary.

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