NICE National Institute for Health and Care Excellence

2021 exceptional surveillance of menopause: diagnosis and management (NICE guideline NG23)

Surveillance report

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Contents

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Surveillance decision

We will update the NICE guideline on menopause: diagnosis and management.

The update will focus on cognitive behavioural therapy (CBT) for the management of menopausal symptoms in women.

Reason for the exceptional review

The purpose of this exceptional review was to examine any impact on the NICE guideline following publication of the MENOS4 randomised controlled trial: effectiveness of nurse-led group CBT for hot flushes and night sweats in women with breast cancer. We also considered previously identified evidence on CBT as a treatment for vasomotor symptoms, which arose during development and surveillance of the guideline.

Methods

The exceptional surveillance process consisted of:

- Considering the evidence used to develop the guideline in 2015.
- Considering relevant information from the previous surveillance review of the guideline in 2019.
- Considering the new evidence that triggered the exceptional review.
- Feedback from topic experts.

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.

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Information considered in this exceptional surveillance review

Guideline development

At the time of guideline development in 2015 there was limited evidence to make recommendations on nonpharmaceutical treatments for women experiencing menopausal symptoms as a result of breast cancer treatment. This represents an unmet need as NICE recommended treatment of vasomotor symptoms, hormone replacement therapy (HRT), is contraindicated in this population. As a result, the following high priority NICE research recommendation was made to address the gap in the evidence base: what is the safety and effectiveness of alternatives to systemic HRT as treatments for menopausal symptoms in women who have had treatment for breast cancer?

The development committee conjectured that the initial expense of an evidence-based licensed treatment for menopausal symptoms in this population would be offset by reduced visits, and hence burden, on primary and secondary healthcare teams and improved workplace productivity.

One potential non-pharmacological treatment for vasomotor symptoms for all women, including those receiving breast cancer treatment, is CBT. This treatment for menopausal symptoms was identified in both guideline development and surveillance but the evidence base has not been considered in its entirety.

Information considered when developing the guideline

Evidence identified during guideline development for the management of short-term menopausal symptoms, including vasomotor symptoms, identified studies evaluating CBT. To address the review question, 'what is the most clinical and cost-effective treatment for the relief of individual menopause related symptoms for women at menopause?', evidence synthesis was done in 2 ways: a network meta-analysis looking at the control of vasomotor symptoms and a pairwise meta-analysis looking at other short-term menopausal symptoms. The evidence was assessed for groups of women undergoing natural menopause with a uterus, without a uterus and undergoing menopause because of breast cancer treatment.

An evidence search for the network meta-analysis identified 3 trials (Mann et al. 2012

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[MENOS1]), Ayers et al. 2012 [MENOS2], and Duijts et al. 2012) that covered the use of CBT for the treatment of vasomotor symptoms in the menopause. Of the 3 studies identified, 2 related to women with menopausal symptoms who were having breast cancer treatment, and 1 related to women undergoing natural menopause. However, these CBT studies were not included in the final network meta-analysis, as they could not be directly compared with the rest of the evidence.

While the 3 papers identified in 2015 were not included in the analysis, they do report that for women experiencing menopausal vasomotor symptoms, both group and self-help CBT significantly reduced scores on the self-reported hot flush night sweats problem rating scale, in addition to benefits to mood. This was the case for women experiencing menopause as a result of breast cancer treatment and also natural menopause. There were inconsistent changes to the frequency of hot flush night sweats across the studies.

Evidence from 1 of the CBT studies was used in the pairwise meta-analyses looking at control of short-term non-vasomotor symptoms during menopause. Evidence from Mann et al. (2012) was assessed for the outcomes of low mood, anxiety, and frequency of joint and muscle aches and pains. The evidence for low mood and anxiety outcomes, from this 1 study, was considered to be moderate quality and led to recommendation 1.4.6, which states: 'consider CBT to alleviate low mood or anxiety that arises as a result of the menopause'.

The evidence regarding CBT for control of vasomotor symptoms was therefore not considered at the time, for any population of women undergoing menopause.

Information considered in previous surveillance of this guideline

The 2019 surveillance review acknowledged that in addition to effectively treating symptoms of low mood, CBT has been reported to be effective at managing other menopausal symptoms including vasomotor symptoms. Evidence was found both for women undergoing menopause as a result of breast cancer treatment (1 study) and for women undergoing natural menopause (2 studies).

Evidence summaries from the 2019 surveillance review included 3 papers on the use of CBT to treat symptoms of menopause:

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- McCurry et al. 2016 looked at CBT for insomnia compared to menopause education, in women undergoing natural menopause. They found that there was no difference in hot flush night sweats frequency, but there was an improvement in the hot flush related daily interference scale.
- Hardy et al. 2018 looked at women undergoing natural menopause and provided a self-help CBT booklet in a work environment; this was compared to wait list control. This resulted in a significant improvement in both the hot flush night sweats problem rating scale, and hot flush night sweats frequency.
- Atema et al. 2019 looked at women experiencing menopause as a result of breast cancer treatment, and provided internet delivered CBT with or without therapist support, this was compared to wait list control. This resulted in a significant improvement in both the hot flush night sweats problem rating scale and hot flush night sweats frequency.

The decision in 2019 was to not update recommendations concerning CBT for the control of other menopausal symptoms, due to the heterogeneity in the modalities of the CBT delivery.

New published evidence - MENOS4

The MENOS4 study was identified during the 2019 surveillance review of the NICE guideline as relevant ongoing research, which might help address the research recommendation concerning alternatives to systemic HRT as treatments for menopausal symptoms. The MENOS4 study published in 2020 and is being considered under the current exceptional surveillance review. This work is the fourth published MENOS study from a body of research looking into the effect of CBT for the treatment of vasomotor symptoms during menopause, both natural and induced by breast cancer treatment.

MENOS4 study methods

The study is a multi-centre, phase III, individually randomised controlled trial of a breast cancer nurse-delivered group CBT versus treatment as usual (TAU), based within the NHS.

The CBT program was delivered by NHS breast cancer nurses in England and Wales, following 2 days of training by a clinical psychologist. The CBT program consisted of up to 6 weekly 90 minute group sessions, following a structured manual.

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Outcome measures were recorded at 9 and 26 weeks after randomisation. Analyses were based on a modified intention-to-treat population, which excluded participants who contributed fewer than 2 items on the outcome measure. The sample size was established following a power analysis performed to allow them to detect a clinically relevant difference of 2 points on the hot flush night sweats problem rating scale (maximum score of 10).

MENOS4 results

The study recruited 61 women from 6 UK hospitals to the CBT arm and 66 women to the TAU control arm (mean age of women was 53.5 and 55.2 years, respectively for each group).

The key findings of this study include:

- For the primary outcome, hot flush night sweats problem rating scale, there was a 3.2 point (46%) versus 1 point (15%) change for CBT versus TAU at 26 weeks (adjusted mean difference -1.96, confidence interval -3.68 to -0.23, p=0.039).
- Secondary outcomes also showed significant improvements, including frequency of hot flush night sweats, hot flush daily interference scale, sleep quality, anxiety and depression. These improvements were reported at the 9 and 26 week timepoints.
- For the secondary outcome vasomotor symptom frequency at 26 weeks, there was a significant difference between groups: 28% reduction (58 down to 42 flushes per week) in hot flush night sweats incidence in the CBT group compared to an 11% reduction (63 down to 56 flushes per week) in the control group (p=0.010).

Topic expert feedback

In this exceptional review, we engaged with topic experts who were recruited to the NICE Centre for Guidelines Expert Advisers Panel to represent their specialty. We received feedback from 5 topic experts (including an academic, 2 consultant gynaecologists, a consultant breast cancer nurse and a nurse specialising in menopause) with all 5 indicating that the guideline should be updated to take account of the MENOS4 trial.

One expert highlighted that there is current UK work being done to introduce these interventions using the same CBT protocol as the MENOS4 study, for women with natural

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or breast cancer treatment related menopause. However, it was noted that currently the majority of these interventions are funded and enabled by charities, and therefore there may be capacity and funding issues for wider implementation. Wider implementation was also raised as a particular area of concern by the consultant breast cancer nurse, especially if the delivery of CBT becomes the responsibility of breast cancer nurses within NHS clinics. One expert suggested that wider implementation of CBT for menopausal symptoms should be limited to women for whom HRT is contraindicated, such as those with breast cancer. Within the body of evidence previously identified, multiple modalities have been shown to have positive effects on the hot flush night sweats problem rating scale however, including a self-help CBT booklet. The update will therefore need to consider which modality is most suitable to wider implementation.

Two consultant gynaecologists and a consultant breast cancer nurse highlighted the importance of health economic analysis to establish whether this was a cost-effective intervention; and this should be evaluated by NICE in any future update plans. One expert also highlighted that the majority of studies that have been published in this area use the structured manual used in MENOS4, the study under consideration in this exceptional review.

Equalities

At the time of guideline development, the following equality issue was identified: women with hormone-sensitive cancer are a group in need of special consideration; increasing survival rates should be accompanied by appropriate survivorship management. Women with hormone-sensitive cancers are rarely offered hormonal treatment for menopausal symptoms but the available alternatives are less effective. This is therefore a particular area of unmet clinical need for this population of women.

Overall decision

This exceptional review considered MENOS4, a UK based randomised control trial that compared CBT against TAU, for women experiencing menopausal symptoms due to breast cancer treatment. It found significant improvements in the hot flush night sweats problem rating scale, as well as improvements in frequency of hot flush night sweats, hot flash daily interference scale, sleep quality, anxiety and depression. All improvements were reported at the 9- and 26-week timepoints.

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During this exceptional surveillance review we have also looked at how CBT for vasomotor symptom control was considered during initial guideline development. While CBT for vasomotor symptom control was identified as a potential treatment, it was not analysed in comparison with other treatments, such as HRT, due to disconnection from the network meta-analysis. As a result, the efficacy of CBT for vasomotor symptom control was not considered for any population of menopausal women.

Additions to the evidence base for CBT for vasomotor symptom control were identified during the 2019 surveillance review of the guideline. An update was not recommended at that time due to the differing modalities of CBT delivery across the identified evidence. However, 1 of the topic experts in the current review raised the point that while these studies deliver CBT in a range of modalities the programme and the protocol informing delivery is the same across almost all studies mentioned within the current exceptional review (with 1 exception, a trial which delivered CBT for insomnia).

Due to the increasing evidence base, and absence of a complete analysis of all available literature, we consider it is important to establish the efficacy and cost effectiveness of CBT for vasomotor symptom control. While the use of CBT to control vasomotor symptoms could be especially important if safe and effective for women experiencing menopause symptoms due to breast cancer treatment, the evidence base also includes women undergoing natural menopause, as does the relevant review question. It is therefore of interest to establish whether this treatment could also be appropriate for women undergoing natural menopause for whom HRT is undesirable or intolerable.

Following consideration of the results from the MENOS4 study, previous evidence, as well as topic expert feedback, and consideration of how past analysis was conducted, the new evidence is directly relevant to the recommendation for research (what is the safety and effectiveness of alternatives to systemic HRT as treatments for menopausal symptoms in women who have had treatment for breast cancer?) and to the original review question and may have an impact on the guideline. The results of a complete analysis of the efficacy of CBT to treat vasomotor symptoms in women undergoing menopause as a result of breast cancer treatment may also impact on NICE's guidelines on early and locally advanced breast cancer and familial breast cancer. During the update consideration will be given to any implications on other NICE guidelines.

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