The use of a screening tool in primary care to identify menopausal and perimenopausal women who could benefit from Hormone replacement therapy

Introduction

The menopause represents a normal physiological change that occurs on average occurs in women age 50. Though not strictly an illness, the low levels of oestrogen associated with the menopause commonly results in vasomotor symptoms such as hot flushes and night sweats. In addition, some also experience sleep disturbance, depression, mood changes, musculoskeletal pain, vaginal dryness and low libido.[1] Furthermore, some evidence suggests that women who experience more severe menopausal symptoms have a greater prevalence of cardiovascular and osteoporosis risk factors.[2] Though not all women will be affected, it has been estimated that up to 75% of postmenopausal women experience vasomotor symptoms and that the median duration of these symptoms is 7.4 years.[3]

The diagnosis of the menopause is based on clinical symptoms and does not require any confirmatory investigations. A woman is considered to be perimenopausal when she has vasomotor symptoms and irregular periods and a diagnosis of the menopause can be made for any women aged over 45 with amenorrhoea for at least 12 months.

Management of the menopause

The most effective treatment for vasomotor associated menopausal symptoms is hormone replacement therapy (HRT) which can be used either via the oral or transdermal route. In its review, NICE suggested that the transdermal route was both more efficacious and cost-effective at relieving vasomotor symptoms.[1] In addition to vasomotor symptoms, there is evidence from observational studies that HRT can have a positive effect on mood, sexual function and genitourinary symptoms.[3] In the longer-term, HRT has been shown to preserve bone density and thereby reduce the risk of osteoporosis. Additionally, provided that HRT is started within 10 years of the menopause or before 60 years of age, there is also a reduction in cardiovascular disease risk.[4]

In the past, there have been concerns over the potential increased risk for breast cancer and venous thrombosis when using HRT. For instance, the women's health initiative (WHI) found that patients assigned to oestrogen-only HRT, experienced a small reduction in breast cancer risk though in contrast, this risk was slightly elevated in those given oestrogen and progesterone. However, the increased risk appears to be linked to the type of progesterone used. For instance, an analysis of French patients from the E3N Cohort, observed that the use of micronized progesterone was not associated with an increased risk of breast cancer compared to other forms of progesterone.[5] Indeed, a recent systematic review of the literature on impact of micronized progesterone on breast cancer risk concluded that there was limited evidence that combining oestrogen with micronized progesterone do not increase breast cancer risk for up to 5 years of treatment duration.[6]

Assessing symptom severity

A decision on the most appropriate form of treatment depends to some degree on the range and severity of symptoms experienced by the woman. One tool to assess both the range and severity of menopausal symptoms is the Menopausal Rating Scale (MRS) has been extensively validated and can be considered as a menopause-specific, health-related quality of life scale. It consists of 11 items which are self-completed by the women on a 5-point scale from 0 (no symptoms) to 4 (severe symptoms). The MRS consists of 3 domains that cover psychological symptoms, somato-vegetative symptoms (e.g. vasomotor symptoms) and urogenital symptoms. The range of the MRS is 0 (asymptomatic) to 44 (highest level of symptomology). Moreover, the cut-off points on the scale are no/little symptoms (0 – 4), mild (5 – 8), moderate (9 – 15) and severe (16+)[7] and it can therefore be administered to assess the level of symptom severity across the three domains.

Clinical Pharmacists

In the General Pharmaceutical Council's recently published discussion paper on the subject of 'tomorrow's pharmacy team', emphasis is placed on the need for pharmacists to relieve the current pressures in primary care, for example in general medical practices.[8] Recently, NHS England has announced additional funding to extend clinical pharmacists based within general medical practices, providing greater opportunity to care for those with long-term conditions.[9] However, the role of these clinical pharmacists to date has been poorly defined and one area in which they might be able to make an important contribution to patient care is in offering advice and treatment to women with menopausal symptoms.

HRT prescribing

The WHI study described earlier led to a reduction in prescribing of HRT[10,11] and data from the US suggests that rates of prescribing continued to decline and reached 4.7% in 2010.[12] However, a recent survey of 749 Brazilian women found the prevalence of HRT use to be 19.5%.[13] Despite these low levels of HRT, quality of life studies suggest that the impairment with respect to quality of life from menopausal symptoms leads to a significant mental and physical burden compared to women without symptoms.[14] Furthermore in a 2016 survey by Ipsos MORI (for the British Menopause Society) of women aged between 45 and 65, only half had consulted a healthcare professional about their menopausal symptoms and that 42% said that their symptoms were much worse than suspected.[15] The survey also revealed how menopausal symptoms impacted on 50% of women's home life and a third on their work life. Little information is available on the proportion of women receiving HRT in the UK though one study from 2005 found that HRT use was 10 to 11%.[16] These studies suggest a potentially huge burden of unmet need for women experiencing the menopause who are not accessing professional advice or effective treatment for their symptoms, even though the latest thinking is that HRT offers several benefits and that the risks are rare.[17]

In the present study, we therefore propose to make use of practice-based clinical pharmacists to identify women aged between 47 and 53 who are not prescribed HRT (and

have no contra-indications) and invite them to complete the MRS tool. Women who score at least 8 on the MRS scale and who could therefore benefit from HRT to manage their menopausal symptoms, would be offered the opportunity of a consultation with the clinical pharmacist. In addition, we will determine the baseline impact of menopausal symptoms on quality of life using a specific menopausal quality of life (MenQol) questionnaire.[18]

The study has the potential to involve clinical practice-based pharmacists in the management of women with menopausal symptoms and to ensure that they are able to make an informed choice on the use of HRT and are managed in accordance with the NICE guideline.

Aim

To make use of the MRS tool to identify women with menopausal symptoms that could benefit from Hormone replacement therapy

Objectives

Primary objectives relating to patient outcomes

- *To determine the range and severity of menopausal symptoms (based on the MRS scale) experienced by women aged between 47 and 53*
- *To measure changes in women's self-reported MRS scores 3 months after initiating HRT therapy*
- *Changes in MenQol scores 3 months after initiating HRT therapy*

Secondary outcomes relating to study processes

- *The rate of uptake of HRT from eligible patients*
- *To determine the number of women eligible for HRT therapy identified from the MRS scale*
- *The number of eligible women decline HRT after a discussion with the clinical pharmacist*
- *The number of women dropping out of the study due to adverse effects of HRT therapy*
- *Any changes to women's other medicines once prescribed HRT e.g. antidepressants*

Method

Design

This will be an uncontrolled before and after intervention study.

Setting

Women recruited from primary care

Inclusion criteria

- Women aged between 47 and 53 currently not prescribed any form of HRT therapy

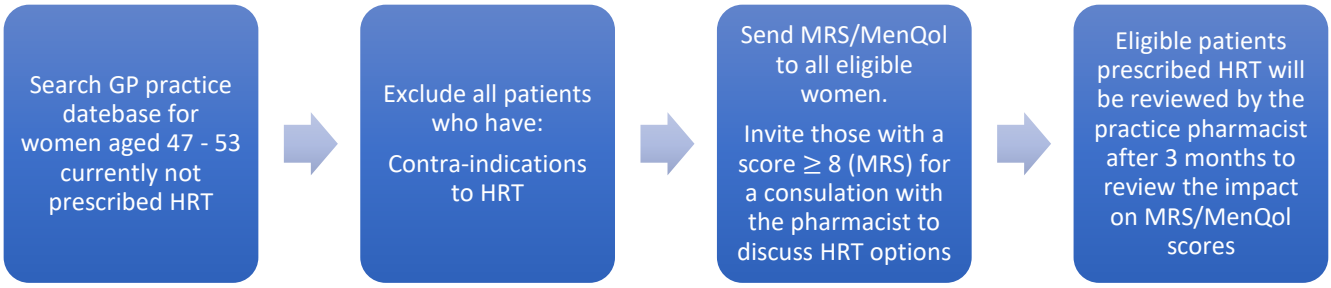
- Women who are perimenopausal or menopausal, i.e. whether they have ceased or are having changes to their periods.

Exclusion Criteria

- Women who have contra-indications to the use of HRT including:
    a) Current, past or suspected breast cancer
    b) Known or suspected oestrogen-sensitive cancer
    c) Undiagnosed vaginal bleeding
    d) Untreated endometrial hyperplasia
    e) Previous idiopathic or current venous thromboembolism unless already on anticoagulant therapy
    f) Untreated hypertension
    g) Active liver disease or abnormal liver function tests
    h) Pregnancy

Patient identification

The protocol in the flow-diagram below illustrates how women will be identified for inclusion into the study.



Proposed route for the identification of suitable patient

Recruitment/Data collection

1. A study poster will be used to advertise the study in GP sites
2. Patients identified from the search of the practice database will be sent an invitation to take part by text, email or post, with a link to the information leaflet, consent form and copies of the MRS/MenQol scales

3. The practice (administrative staff) will collate the completed MRS/MenQol forms and invite those with a score ≥ 8 (on the MRS) for an appointment with the practice pharmacist to discuss use of HRT.
4. Eligible patients willing to use HRT will be invited back for an optional online follow-up appointment after 3 months to review the impact of HRT on MRS and MenQol scores
5. Practices will be asked to record the number of patients identified in the database search/current treatments/ non-responders/refusals
6. The practice staff will collate details of patient demographics/current treatment onto an anonymised data collection form
7. Any known adverse effects reported by women will be documented and new or unrecognised effects will be reported using the yellow card scheme.

Pharmacist training

To ensure that all participating clinical pharmacists are prepared to participate in the study, we will produce a bespoke training pack that will cover background information on the menopause, symptomology and any national guidance around treatment recommendations and information to help complete the study paperwork. The Clinical oversight of the decisions made by the pharmacists will be lie with the patient's General Practitioner. Furthermore, before, during or after the results from the questionnaires or in consultation any signs and symptoms of mood disorder will be flagged to the GP and followed up using the yellow card system.

Sample size calculation

In a validation study conducted in 9,311 women, the mean pre-treatment MRS score prior to HRT therapy was 11 with an absolute change in score of 9.3 (± 7.4).[7] In further work, the same group determined that a 4-point difference in MRS scores was sufficient to establish a clinical relevant effect of treatment.[19] These data provide an effect size of 0.54 (4/7.4) and using Gpower with a two-tailed test, alpha level of 0.05 with 95% power, would require a total sample of 47 women to detect this effect. Since there is some degree of uncertainty about the potential attrition rate for this study, assuming a 25% rate would require approximately 60 women.

We will undertake an initial search in one practice to determine the actual number of eligible patients and use this information to determine the potential number of practices required for the study to achieve a target of 60 women. For this feasibility study the maximum number of practices will be no more than 3. Following recruitment at the first two practices an interim analysis will be undertaken to determine whether further a practice is required to achieve the target number of participants.

Outcome measures

The primary outcome measure will be the proportion of eligible women who are subsequently prescribed HRT

Secondary outcome measures:

- The number of eligible women screened using the MRS tools
- The number of women with an MRS score of at least 8 (upper limit of mild symptoms)
- The mean change in total MRS scores after 3 months of HRT therapy
- The mean change in total MenQol score after 3 months of HRT therapy
- Any changes to other currently prescribed treatments that may be related to the management of menopausal symptoms

Data Analysis

Both demographics and current treatments used by women will be analysed descriptively. Means and standard deviations will be used for normally distributed continuous variables, medians and interquartile ranges will be used for non-normally distributed continuous variable, and counts and percentages will be used to describe categorical variables.
Data generated from the post treatment interviews will also be analysed thematically.
Changes in total MRS/MenQol scores will be assessed using paired t-tests if the data are normally distributed or non-parametric equivalents if the data are skewed.

Governance

We will ensure that the study receives NHS Ethics Committee and Health Research Authority approval and that all women who participate provide written, informed consent to participate in the study.

Funding and Sponsorship

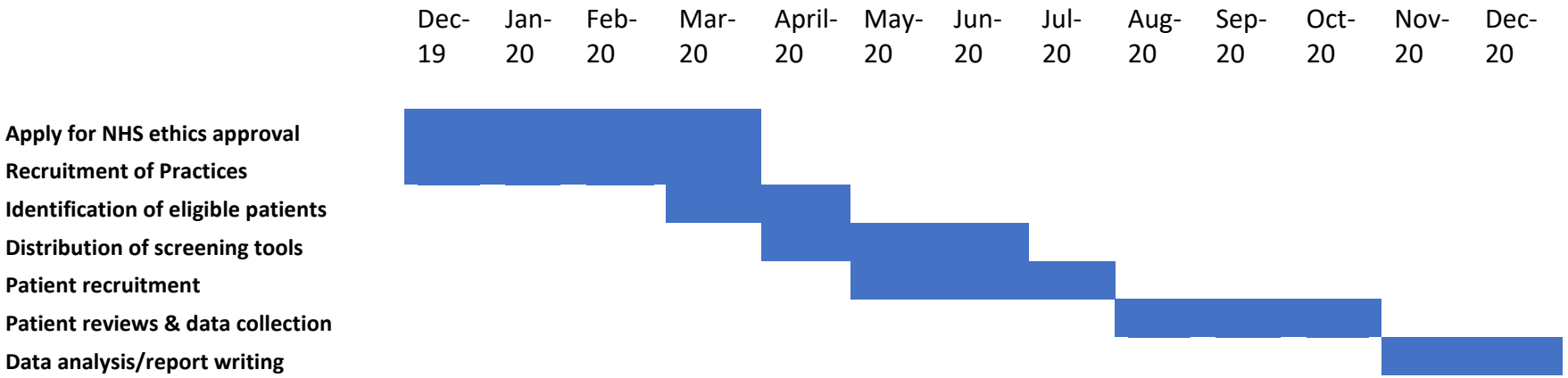
The study has been funded by a research award from Besins Heathcare Limited.
Although they are funding the research they have not prescribed which HRT treatment women will be offered and will not access any identifiable patient data.
The study is sponsored by Rotherham Doncaster & South Humber NHS Trust.

Dissemination

We will aim to produce academic publications based on the results of the study and to distribute the findings through the primary care menopause society. In addition, we will aim to discuss the results at primary care pharmacy conferences.

Timescale

We anticipate that the study will commence once ethical approval has been received which will hopefully be around September 2019



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