Maturitas 80 (2015) 273–281

Contents lists available at ScienceDirect

Maturitas

journal homepage: www.elsevier.com/locate/maturitas

Qualitative cross-cultural exploration of breast symptoms and impacts associated with hormonal treatments for menopausal symptoms to inform the development of new patient-reported measurement tools

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ARTICLE INFO

Article history:
Received 9 October 2014
Received in revised form
25 November 2014
Accepted 26 November 2014

Keywords:
Qualitative
Instrument development
Patient-reported outcomes

ABSTRACT

To explore cross-cultural experiences of women taking estrogen plus progestin therapies (EPT) and develop a symptom-based electronic diary and impact questionnaire for EPT-related breast symptoms.

(1) Concept elicitation interviews were conducted with women in the US ($n = 14$), Italy ($n = 15$), Mexico ($n = 15$) and China ($n = 15$) to explore breast symptoms associated with EPT. Patients completed the Breast Sensitivity Questionnaire (BSQ) to evaluate understanding and comprehensiveness. (2) Based on concept elicitation, a 6-item eDiary (Breast Pain/Tenderness Daily Diary – BPT-DD) was generated and the BSQ modified forming the 18-item Breast Sensations Impact Questionnaire (BSIQ). (3) The measures were pilot-tested and then cognitively debriefed with US women receiving EPT. All qualitative data was subject to thematic analysis.

Concept elicitation identified breast pain/tenderness, swollen breasts and sensitivity to contact as important symptoms, impacting women's emotional well-being, relationships with family/friends, social life, sleep, ability to move freely, contact, clothing and sexual activity. Experiences were relatively consistent across the country samples. Based on pilot testing and cognitive debriefing, the BPT-DD was reduced to 4 items (and renamed the Breast Pain Daily Diary – BP-DD) and the BSIQ was reduced to 13 items due to conceptual redundancy.

Women taking EPT in the US, China, Mexico and Italy reported breast sensations that have a detrimental impact on quality of life. Two new measures were developed to assess the severity and impact of breast pain specific to EPT. This work highlights that EPT-related symptoms should be part of treatment decision-making, and treatments with less burdensome side effects are needed.

Abbreviations: EPT, estrogen plus progestin therapies; BSIQ, Breast Sensations Impact Questionnaire; BSQ, Breast Sensations Questionnaire; BPT-DD, Breast Pain/Tenderness Daily Diary; HRQL, health-related quality of life; HT, hormone therapy; IGM, Item Generation Meeting; IRB, Independent Review Board; PM, postmenopausal; VMS, vasomotor symptoms.

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http://dx.doi.org/10.1016/j.maturitas.2014.11.019
0378-5122/

1. Introduction

The current standard of care for the treatment of menopausal symptoms in postmenopausal women with a uterus is estrogen plus progestin therapies (EPT). While highly efficacious for preventing osteoporosis and treating vasomotor symptoms and vulvar/vaginal atrophy, EPT is also associated with bothersome side effects, such as vaginal spotting/bleeding and breast tenderness [1]. Breast tenderness is reported to occur significantly more frequently in women receiving combined EPT compared with placebo or conjunctive estrogens alone [2] and is associated with increased mammographic breast density [3] and subsequent breast cancer risk [2]. In randomized clinical trials, incidence of breast tenderness in postmenopausal women after initiation of EPT has been reported to range from approximately 9% to 16% [1,2,4–6]. Many women who experience breast tenderness discontinue treatment, potentially due to concerns or fears of breast cancer [7] following publication of such risk in findings from the Women's Health Initiative trials [8]. Thus, there is evidence to suggest that side effects, specifically related to the breast, and worries about risks, especially breast cancer, associated with EPT can lead to non-adherence or discontinuation of treatment, suggesting there is an unmet need for treatments of menopausal symptoms with less burdensome side effects. To better evaluate the clinical benefit of novel therapies relative to existing therapies, validated patient-reported outcome (PRO) measures are required to assess not only the efficacy of the treatment (in terms of reduction in symptoms), but also any benefits in terms of tolerability.

Following a review of the literature, the Breast Sensitivity Questionnaire (BSQ) was identified as measuring hormone therapy (HT)-related breast symptoms and their impact on health-related quality of life (HRQL). Containing 11 symptom items and 10 impact items, the BSQ was developed in line with regulatory guidance, and involved patient focus groups [9]. However, use of a one-week recall period to assess symptoms that are likely to have daily variation was not considered appropriate because of potential recall bias. Moreover, changing the recall period to 24 hours for the daily assessment of 11 symptom items would represent a significant burden on patients and increase the risk of missing data. Thus there was a need to develop a new breast symptom assessment that included a 24 hour recall period and could be feasibly completed as a daily diary.

Additionally, focus groups conducted to inform the BSQ's development were only conducted in the United States (US); given the cultural differences in the experience of menopausal symptoms and impacts [10,11], the BSQ's content validity for women outside of the US was unknown. Thus further evaluation of the BSQ was conducted in culturally diverse countries (Italy, Mexico and China) to evaluate the appropriateness of the BSQ impact items as a potential measure of EPT-related breast symptom impact, alongside qualitative concept elicitation interviews to support the development of the new daily breast symptom diary.

2. Methods

2.1. Overview of study

This paper summarizes findings from a three stage qualitative study (Fig. 1) to explore the two most common side effects experienced by postmenopausal women across different cultures taking EPT: vaginal bleeding/spotting and breast sensations (specifically breast pain/tenderness). This paper reports findings for breast sensations; findings on the symptoms and impacts of vaginal bleeding/spotting as a side effect of EPT are published in a separate companion paper [12]. In Stage 1, open-ended, exploratory concept elicitation interviews with women in the US, Italy, Mexico and China were conducted to explore postmenopausal women's descriptions of breast sensations associated with EPT and their impact on HRQL. The BSQ was also cognitively debriefed to assess its comprehensiveness as a measure of the impact of breast sensations associated with EPT. Stage 2 consisted of simultaneous item generation of a daily breast sensations symptom assessment (Breast Pain/Tenderness Daily Diary, BPT-DD) in four languages (Italian, Mexican, Chinese, US-English), using findings from Stage 1 and input from measurement experts, clinical experts and linguists. Modifications to the impact items of the BSQ were also made based on the interview findings. The involvement of linguists and interviewers ensured item wording was developed or modified to reflect the natural language of postmenopausal women from each of the four countries studied, ensuring the items had cross-cultural validity and will be easily translatable and conceptually equivalent in other potential languages. Both the BPT-DD and the modified BSQ (referred to as the Breast Sensations Impact Questionnaire [BSIQ]) were then subjected to full cognitive debriefing in US-English in Stage 3.

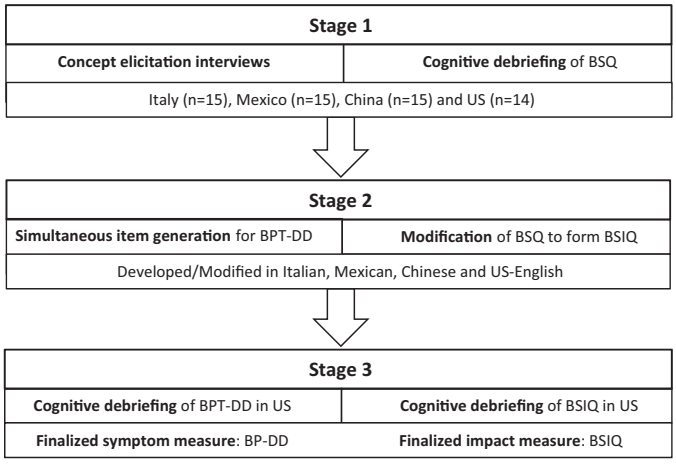

Fig. 1. Overview of study. *Note*: BPT-DD: Breast Pain/Tenderness Daily Diary, BP-DD: Breast Pain Daily Diary, BSQ: Breast Sensitivity Questionnaire, BSIQ; Breast Sensations Impact Questionnaire.

2.2. Recruitment

In Stage 1, postmenopausal women receiving EPT were recruited from the US, Italy, Mexico and China. In Stage 3, women were recruited from two sites in the US only, via primary care physicians/general practitioners or gynecologists. Inclusion criteria for the study included postmenopausal women who had an intact uterus, were taking EPT and had experienced breast pain/tenderness on at least 2 days during the previous 4 weeks. In both interview stages, sampling quotas for age, education, ethnicity, clinical characteristics (severity of breast pain/tenderness) and treatment history (time on EPT) were used for each country.

2.3. Interview procedures

All interviews were conducted by experienced qualitative interviewers using a semi-structured interview guide. In Stage 1, the interview guide questions started with open-ended, non-leading questions to capture spontaneous mentions of concepts related to women's experiences of breast sensations as a result of EPT. Following the open-ended questioning, the BSQ was cognitively debriefed using a 'think aloud' [13] approach where each participant was asked to speak aloud their thoughts as they read each instruction and completed each item. This was followed by detailed