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Qualitative cross-cultural exploration of vaginal bleeding/spotting symptoms and impacts associated with hormone therapy in post-menopausal women to inform the development of new patient-reported measurement tools

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ABSTRACT

Objectives: To understand the vaginal bleeding/spotting experiences of postmenopausal (PM) women taking estrogen plus progestin therapies (EPT) and develop measures to assess these symptoms and their impact on women's daily lives in four countries.
Design: (1) Concept elicitation interviews were conducted with PM women in the US ($n = 14$), Italy ($n = 15$), Mexico ($n = 15$) and China ($n = 15$) to explore vaginal bleeding/spotting symptoms associated with EPT. The Post-Menopausal Bleeding Questionnaire (PMBQ) was also debriefed to evaluate understanding and comprehensiveness. (2) Based on concept elicitation, a single item electronic daily diary was developed and the PMBQ modified to form a 12-item impact measure. (3) The measures were pilot-tested and then cognitively debriefed with US women receiving EPT. All qualitative data was subject to thematic analysis.
Main outcome measures: The Vaginal Bleeding/Spotting Daily Diary, (VBS-DD) and Post-Menopausal Bleeding Impact Questionnaire (PMBIQ) were developed in this study.
Results: Concept elicitation identified vaginal bleeding and spotting as important symptoms for women taking EPT, impacting their emotional wellbeing, social life, ability to move freely, clothing and sexual activity. Based on pilot testing and cognitive debriefing, women demonstrated good understanding of the VBS-DD and the PMBQ was reduced to 10 items due to conceptual redundancy.
Conclusions: Women taking EPT in the US, China, Mexico and Italy reported vaginal bleeding/spotting symptoms that have a detrimental impact on their quality of life. Two new measures were developed to assess the severity and impact of vaginal bleeding/spotting specific to EPT. This work highlights the need for EPT-related symptoms to be a part of treatment decision-making.

Abbreviations: PM, postmenopausal; EPT, estrogen plus progestin therapies; PMBQ, Post-Menopausal Bleeding Questionnaire; VBS-DD, Vaginal Bleeding/Spotting Daily Diary; PMBIQ, Post-Menopausal Bleeding Impact Questionnaire; VMS, vasomotor symptoms; VVA, vaginal atrophy; IGM, Item Generation Meeting; PMBIQ, Postmenopausal Bleeding Impact Questionnaire; IRB, Independent Review Board; HRQL, health-related quality of life.

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1. Introduction

It is estimated there are over 166 million postmenopausal women in the US, Japan and the European Union (EU) [1]. Due to decreasing levels of estrogens at menopause, women often experience bothersome vasomotor symptoms (VMS), vulvar and vaginal atrophy (VVA), and an increased risk of osteoporosis [2]. There appear to be cultural differences in the manner and degree to which menopausal symptoms are reported [3]. Hot flushes are recognized as a symptom directly associated with menopause within the Western biomedical health framework. However in other cultures, such as Japan, while thermoregulation problems are reported, these tend to be experienced as chills and shivers [4].

Estrogen plus progestin therapies (EPT) represent the current standard of care for the treatment of menopause symptoms in postmenopausal women with a uterus. While estrogens have shown success for treating climacteric symptoms, the presence of progestin is necessary to prevent endometrial proliferation [5]. However, progestins in EPT are associated with side effects such as breast pain/tenderness and vaginal spotting/bleeding [6]. Irregular bleeding and spotting is reported to occur in approximately 50% of women receiving continuous EPT [7]. These side effects can result in women permanently discontinuing EPT and have been associated with impairments in quality of life [8] and increased healthcare resource utilization (an estimated 32,000–42,000 postmenopausal women in the US were investigated for abnormal bleeding associated with EPT in 2010 [9]).

Clinical trials aimed at evaluating the clinical benefit of novel therapies relative to existing therapies require reliable and culturally valid measures that assess not only the efficacy of the treatment (in terms of reduction in symptoms), but also benefits in terms of tolerability. A literature review identified no suitable symptom measures, but the Postmenopausal Bleeding Questionnaire (PMBQ) was identified via personal communication as a potentially appropriate impact measure. However, while the PMBQ was well-developed based upon patient focus groups, further content validity testing was deemed necessary to establish the appropriateness of the measure for these particular patient populations, which seemingly has not occurred since there is no reference to the measure in the public domain, currently. This paper thus describes qualitative research to explore patients' experiences of vaginal bleeding/spotting associated with EPT to inform the development of a symptom measure of vaginal bleeding/spotting and to evaluate the content validity of a vaginal bleeding/spotting impact measure.

2. Methods

2.1. Overview of study

This paper reports the qualitative research findings from a three-stage study (Fig. 1). Although the study explored the experiences and impacts of two common EPT side effects, namely vaginal bleeding/spotting and breast sensations, this paper focuses on the findings for vaginal bleeding and spotting only.

In Stage 1, concept elicitation interviews with women from culturally diverse backgrounds were used to understand how postmenopausal women describe the symptoms of bleeding and spotting associated with EPT and their related impacts. During this stage, an existing measure, the Postmenopausal Bleeding Questionnaire (PMBQ) was also cognitively debriefed with participants to assess its content validity as a measure of symptoms and impacts of vaginal bleeding.

Stage 2 consisted of an Item Generation Meeting (IGM) where, using findings from Stage 1, a vaginal bleeding/spotting symptom assessment (Vaginal Bleeding/Spotting Daily Diary – VBS-DD) appropriate for inclusion in clinical trials as a measure of treatment benefit for new menopausal therapies was developed. Input was sought from measurement experts, clinical experts and linguists so that item content could be developed simultaneously in the four languages (Italian, Mexican, Chinese, US-English) using natural language which was easily translatable and conceptually equivalent in each language. In addition, modifications to the PMBQ were also made based on the initial cognitive debriefing in Stage 1, once permission had been granted by the original developer of the instrument. Both the symptom assessment and the modified PMBQ (now referred to as the Postmenopausal Bleeding Impact Questionnaire [PMBIQ]) were then subject to full cognitive debriefing in Stage 3 in the US only.

2.2. Patient recruitment

In Stage 1, interviews were conducted with postmenopausal women receiving EPT in the US ($n = 14$), Italy ($n = 15$), Mexico ($n = 15$) and China ($n = 15$). Sample sizes were devised in consideration of what would be required to achieve conceptual saturation [10]. In Stage 3, participants were all recruited from two locations in the US. Eligible postmenopausal women had to have an intact uterus and were taking EPT with at least 12 months of spontaneous amenorrhea or 6 months of spontaneous amenorrhea with serum follicle-stimulating hormone (FSH) levels >40 mIU/mL prior to EPT. Participants were required to have experienced an episode of vaginal bleeding or spotting on at least 2 days during the preceding 4 weeks.

2.3. Interview procedures

The interviews were conducted by trained qualitative interviewers using a semi-structured interview guide (Appendix A). In Stage 1, the interview guide questions started open-ended to capture spontaneous mentions of concepts related to women's experiences of vaginal bleeding/spotting as a result of EPT. Following this exploratory questioning, the PMBQ was subjected to cognitive debriefing using a 'think aloud' [11] exercise. This involved the patient being asked to speak aloud her thoughts as she read each instruction and completed each item, followed by detailed questions about definitions/meanings, understanding/clarity and relevance.

In Stage 3, US-English participants attended two visits: at Visit One, the PMBIQ was debriefed using a 'think-aloud' approach. The women were then trained to complete the VBS-DD on a hand-held electronic device (eDiary) and took it home to complete as part of a pilot testing for 12–14 days. At Visit Two the women were cognitively debriefed on the VBS-DD and their experience of completing the eDiary.

2.4. Ethics

The study was conducted in accordance with the Declaration of Helsinki and was approved by an Independent Review Board (IRB) in the US for Stages 1 and 2. In Stage 1, ethical approval was also obtained in Italy and Mexico; ethical approval for a study of this nature was not required in China. Written informed consent was obtained from all participants prior to data collection.

2.5. Analysis

In both interview stages, a qualitative analysis software package (Atlas.Ti) was used to facilitate a thematic analysis of verbatim interview transcripts [12]. Non-English transcripts were translated and all analyses were performed in English. In Stage 1, methods of content thematic analysis were used where verbatim quotes

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