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Qualitative research to explore women's experience of vasomotor symptoms and evaluate the suitability of patient-reported outcomes

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BACKGROUND

> The menopause transition reflects the natural decline of follicular estrogen production, resulting in a postmenopausal state with low estradiol levels and permanent absence of menstruation.[1] Menopause can also be induced by medical intervention (e.g., adjuvant endocrine therapy [AET]) resulting in a sudden drop of estrogen levels.[2]

> Vasomotor symptoms (VMS) , commonly referred to as hot flashes, are the leading cause for seeking medical attention during this phase of a woman's life[3] and can have significant impacts on health-related quality of life (HRQoL), including sleep and emotional wellbeing.[4-6,7,8] VMS are therefore considered a patient priority for treatment and there is a growing focus on the development of pharmacological and non-pharmacological treatments.[9,10]

> Clinical-outcome assessments (COAs) are used in VMS clinical trials to assess treatment benefit and support regulatory product labelling claims. To be considered "fit for purpose", COAs must demonstrate evidence supporting content validity in the specific population of interest.[11] To do this, it is imperative that qualitative research is conducted with the target population, to identify relevant concepts of interest and demonstrate understanding and the adequate assessment of concepts through COAs.[11-14]

> To date there is little published qualitative evidence documenting the experience of VMS from the perspective of women and limited evidence supporting the content validity of patient-reported outcomes (PROs) for this specific population.[15]

OBJECTIVES

> To obtain in-depth insights into the experience of VMS, including exploration of associated signs, symptoms and impacts of VMS on HRQoL.

> To evaluate the content validity of the Hot Flash Daily Diary (HFDD), PROMIS Sleep Disturbance Short Form 8b (PROMIS SD SF 8b),[16] and Menopause-Specific Quality of Life (MENQOL)[17] questionnaires, and to determine whether the wording of instructions, definitions, and items are consistently understood, and adequately assess concepts of interest.

> To obtain preliminary insights regarding the degree of change in scores on the HFDD that participants consider to be meaningful.

METHODS

> Twenty participants experiencing moderate to severe hot flashes (N=20) were recruited from four geographically diverse locations in the US (California, Illinois, Maryland, Missouri), including n=10 postmenopausal women (hereafter referred to as 'PM participants') and n=10 women treated with AET (hereafter referred to as 'AET participants').

> Semi-structured, qualitative concept elicitation and cognitive interviews were conducted in line with regulatory standards and best practices.[12-14,18] Open-ended questioning and follow-up probes were used to elicit concepts related to the VMS experience. Participants then completed the PROs (see Table 1 for PRO descriptions) using a 'think aloud' technique, with follow-up questions to assess the content validity of each PRO including questions on item understanding and relevance, and what would constitute a meaningful change in the frequency of hot flashes as a result of hypothetically assumed treatment efficacy.

> Verbatim interview transcripts were qualitatively analysed in Atlas.ti using framework analysis methods.

Table 1. Description of PROs

PRO	Description
HFDD	The HFDD is a diary completed twice daily (morning and evening) to assess the number of mild, moderate and severe hot flashes experienced during the night and during the day, to assess the number of night-time awakenings and the severity of sleep disturbances due to hot flashes occurring at night.
PROMIS SD SF 8b[16]	The PROMIS SD SF 8b is an 8-item instrument that assesses sleep disturbances over the past 7 days.
MENQOL[17]	The MENQOL is a 29-item instrument that assesses the presence and degree of bothersomeness of menopausal symptoms and the impacts on HRQoL in the past week.

RESULTS

Sample characteristics

> The key demographic and clinical characteristics are provided in Table 2.

Table 2. Demographic and clinical characteristics of participants

Demographic and clinical characteristics	PM participants (n=10)	AET participants (n=10)	Total (N=20)
Age in years, mean (min, max)	56.7 (46, 64)	46.2 (26, 58)	51.5 (26, 64)
Ethnicity, n (%)			
Non-Hispanic or Non-Latino	5 (50.0%)	8 (80.0%)	13 (65.0%)
Hispanic or Latino	5 (50.0%)	2 (20.0%)	7 (35.0%)
Race, n (%)			
White	5 (50.0%)	5 (50.0%)	10 (50.0%)
Black/African American	4 (40.0%)	3 (30.0%)	7 (35.0%)
Other (Hispanic)	1 (10.0%)	2 (20.0%)	3 (15.0%)
Menopausal status, n (%)			
Premenopausal	N/A	3 (30.0%)	3 (15.0%)
Perimenopausal	N/A	2 (20.0%)	2 (10.0%)
Postmenopausal	10 (100%)	4 (40.0%)	14 (70.0%)
Unknown	N/A	1 (10.0%)	1 (5.0%)
Duration experiencing hot flashes, n (%)			
<6 years	4 (40.0%)	8 (80.0%)	12 (60.0%)
6-10 years	6 (60.0%	1 (10.0%)	7 (35.0%)
>10 years	0 (0%)	1 (10.0%)	1 (5.0%)

"I wake up and I'm sweating. I can't sleep good. I have to turn the fan, open the window" (PM participant)

"There's probably not a day that goes by that I don't have some type of hot flash… I would probably say that I have more than five, upwards of like maybe seven hot flashes a day." (AET participant)

Concept elicitation

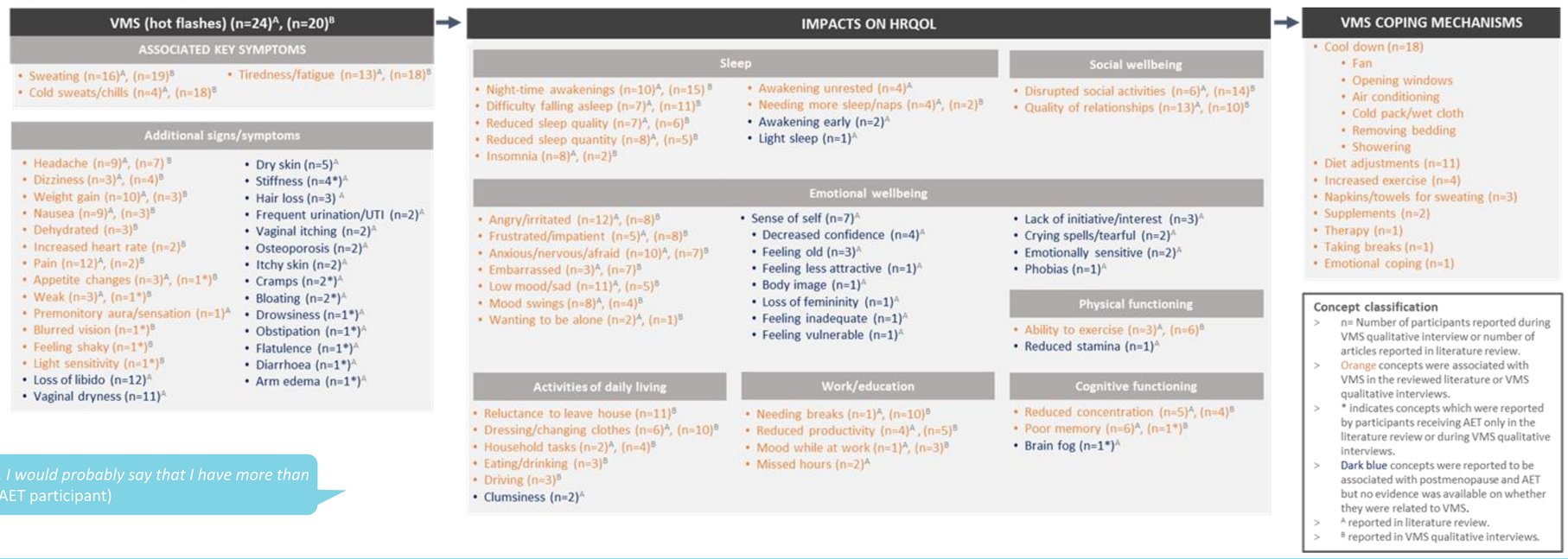
> Sixteen symptoms relevant to VMS (hot flashes) were identified. Associated key symptoms included sweating, cold sweats/chills, and tiredness/fatigue. VMS (hot flashes) were reported to impact HRQoL, including impacts on sleep, emotional wellbeing, social wellbeing, activities of daily living (ADL), work/education, physical and cognitive functioning.

> The presentation and experience of VMS (hot flashes) and associated key symptoms, including the frequency, duration, and/or severity, was broadly similar across the PM and AET participants.

> Concept saturation was considered achieved for the key symptoms and impacts of relevance to this population.

> Results from the concept elicitation interviews were used to refine the draft conceptual model, preliminarily developed using the qualitative literature review conducted previously (see Figure 1).[15]

Figure 1. Refined conceptual model for assessment of VMS (hot flashes)



Cognitive interviews

Understanding

> Most participants asked demonstrated a clear understanding of the HFDD (≥86.7%), PROMIS SD SF 8b (100%) and MENQOL (≥95.0%) items including the recall period, response options and associated instructions.

Figure 2. Overview of relevance of the HFDD

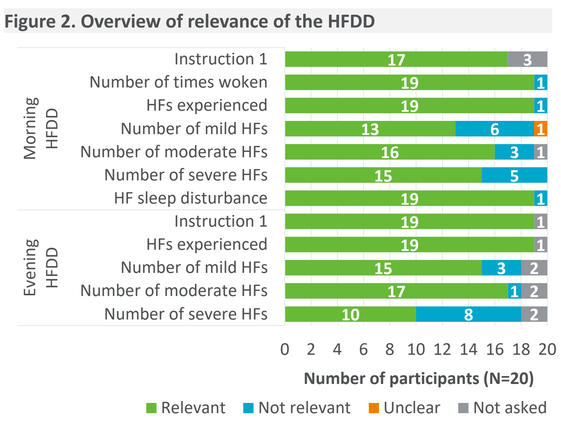


Figure 3. Overview of relevance of PROMIS SD SF 8b

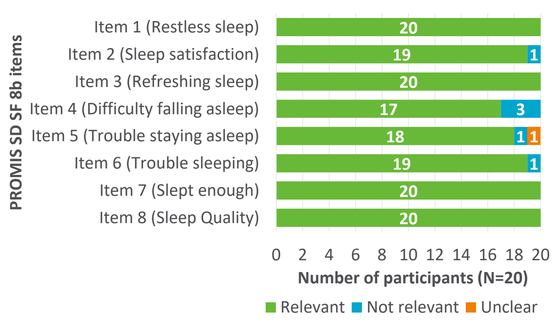
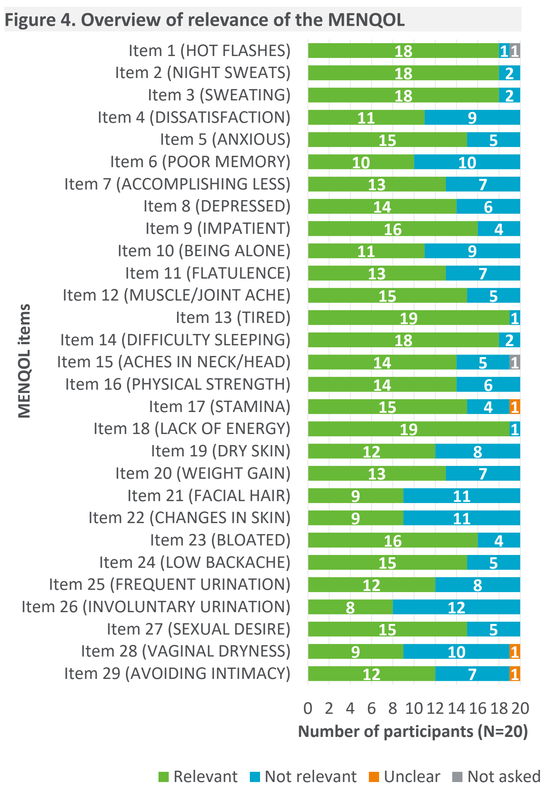


Figure 4. Overview of relevance of the MENQOL



Relevance

> All HFDD items were considered relevant to over half of all participants asked (≥55.6%; Figure 2).

> Most participants (≥85.0%) found each PROMIS SD SF 8b item relevant to their experience (Figure 3).

> Majority of MENQOL items were considered relevant to the participants asked (≥55.0%), with the exception of five items that were less relevant to participants asked (Figure 4). Most of these five items were within the MENQOL Physical Domain (items 11-26), where it is plausible that individual PM and AET participants only experience a subset of the physical symptoms described for menopausal women in general.[19]

> No notable differences in findings were observed between PM and AET-treated women.

Meaningful Change

> A reduction of one moderate or one severe hot flash within a 24-hour period, as assessed by the HFDD, was considered to be a meaningful improvement from treatment to most participants asked (≥80.0%; Figures 5 and 6).

Figure 5. Meaningful change for moderate hot flashes in 24hrs

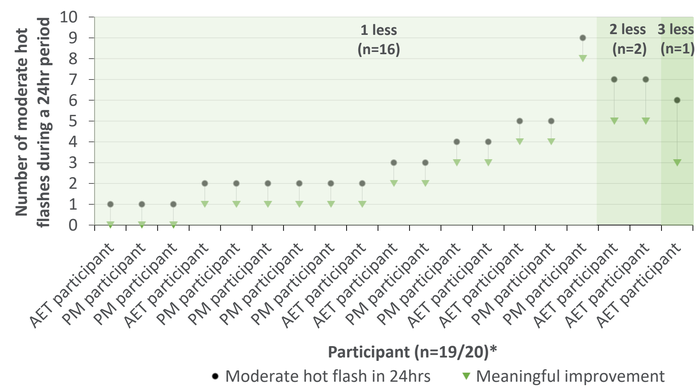
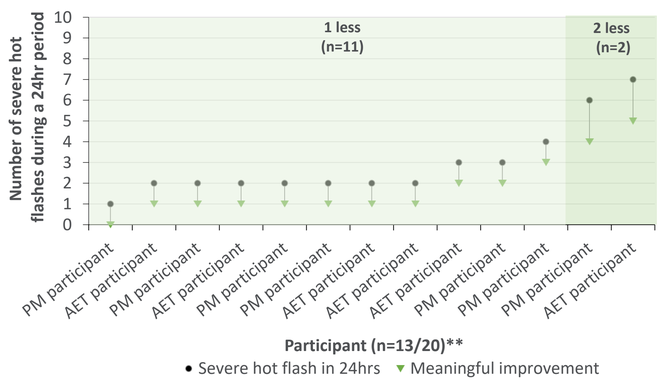


Figure 6. Meaningful change for severe hot flashes in 24hrs



**n=1 participant reported that a reduction of two moderate hot flashes would be meaningful to her but did not report how many moderate hot flashes this would be reduced from when thinking about a previous 24-hour period. **n=6 participants reported that a reduction of one severe hot flash would be meaningful to them but did not report how many severe hot flashes this would be reduced from when thinking about a previous 24-hour period. The remaining n=1 participant did not provide a response when asked.*

"I would probably be able to have more energy through the day, wouldn't be waking up so tired. Um, I'd be able to sleep better, so it would be a huge relief." (PM participant)

"I could get rid of the hot flash, then it would be worth my time. Um, it would probably let me accelerate to do a lot more things in a day's time." (AET participant)

CONCLUSIONS

> Findings provide an in-depth exploration and rich qualitative data on VMS (hot flashes), associated symptoms and impacts on HRQoL reported by women, beyond that presently available in the published literature and thus were used to refine the existing conceptual model.[15]

> In accordance with regulatory guidance,[11-14] findings support the content validity of the HFDD, PROMIS SD SF 8b, and MENQOL for the use in VMS clinical trials. The new evidence builds upon previous work supporting the content validity of the PROMIS SD SF 8b[20] and MENQOL[17] in menopausal women and provides further assurances also for the appropriateness of the PROs for women treated with AET experiencing VMS, which has not been published in the literature to date.

> Further research to evaluate the psychometric validity of the PROs is underway and will support their use in VMS clinical trials to assess treatment effect.

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