Qualitative research to explore women's experience of vasomotor symptoms and evaluate the suitability of patientreported 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 life³ 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

> 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.

OBJECTIVES

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

METHODS

Table 1. Description of PROs > Twenty participants experiencing moderate to severe hot flashes (N=20) were recruited from four

PRO geographically diverse locations in the US (California, Illinois, Maryland, Missouri), including n=10 HFDD 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 se 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.



Description



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ROMIS SD F 8b ¹⁶	The PROMIS SD SF 8b is an 8-item instrument that assesses sleep disturbances over the past 7 days.
1ENQOL 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.

time awakenings and the severity of sleep

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-

disturbances due to hot flashes occurring at night.



Sample characteristics

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

Table 2. Demographic and clinical characteristics of participants				participants. > Concept saturation was considered achieved for the key symptoms and impacts of relevance to this population.						
Demographic and clinical characteristics	PM participants (n=10)	AET participants (n=10)	Total (N=20)	> Results from the cor	ative literature review conduc					
Age in years, mean (min, max)	56.7 (46 <i>,</i> 64)	46.2 (26, 58)	51.5 (26, 64)	previously (see Figure Figure 1. Refined conceptual n						
Ethnicity, n (%) Non-Hispanic or Non-Latino Hispanic or Latino	5 (50.0%) 5 (50.0%)	8 (80.0%) 2 (20.0%)	13 (65.0%) 7 (35.0%)	VMS (hot flashes) ASSOCIATED KEY	(n=24) ^A , (n=20) ^B	▶	IMPACTS ON HRQOL			
Race, n (%) White Black/African American Other (Hispanic) Menopausal status, n (%)	5 (50.0%) 4 (40.0%) 1 (10.0%)	5 (50.0%) 3 (30.0%) 2 (20.0%)	10 (50.0%) 7 (35.0%) 3 (15.0%)		 Tiredness/fatigue (n=13)^A, (n=18)^B ns/symptoms Dry skin (n=5)^A Stiffness (n=4*)^A Hair loss (n=3)^A Frequent urination/UTI (n=2)^A Vaginal itching (n=2)^A Osteoporosis (n=2)^A Itchy skin (n=2)^A Cramps (n=2*)^A Bloating (n=2*)^A 	 Night-time awakenings (n=10)^A, (n=15)^B Difficulty falling asleep (n=7)^A, (n=11)^B Reduced sleep quality (n=7)^A, (n=6)^B Reduced sleep quantity (n=8)^A, (n=5)^B Insomnia (n=8)^A, (n=2)^B 	 Awakening unrested (n=4)^A Needing more sleep/naps (n=4)^A, (n=2)^B Awakening early (n=2)^A Light sleep (n=1)^A 	Social wellbeing Disrupted social activities (n=6)^A, (n=14)^B Quality of relationships (n=13)^A, (n=10)^B 	 Cool down (n=18) Fan Opening windows Air conditioning Cold pack/wet cloth Removing bedding Showering Diet adjustments (n=11) Increased exercise (n=4) Napkins/towels for sweating (n=3) Supplements (n=2) Therapy (n=1) Taking breaks (n=1) Emotional coping (h=1) Concept classification n = Number of participants reported durin VMS qualitative interview or number of articles reported in literature review. Orange concepts were associated with VMS in the reviewed literature or VMS qualitative interviews. * indicates concepts which were reported by participants receiving AET only in the 	
Premenopausal Perimenopausal Postmenopausal	N/A N/A 10 (100%) N/A	3 (30.0%) 2 (20.0%) 4 (40.0%) 1 (10.0%)	3 (15.0%) 2 (10.0%) 14 (70.0%)			 Angry/irritated (n=12)⁻, (n=8)⁰ 	Emotional wellbeing • Sense of self (n=7) ^A	 Lack of initiative/interest (n=3)^A 		
Unknown Duration experiencing hot flashes, n (%) <6 years 6-10 years >10 years	4 (40.0%) 6 (60.0%	1 (10.0%) 8 (80.0%) 1 (10.0%) 1 (10.0%)	1 (5.0%) 12 (60.0%) 7 (35.0%) 1 (5.0%)			 Frustrated/impatient (n=5)^A, (n=8)^B Anxious/nervous/afraid (n=10)^A, (n=7)^B Embarrassed (n=3)^A, (n=7)^B Low mood/sad (n=11)^A, (n=5)^B Mood swings (n=8)^A, (n=4)^B Wanting to be alone (n=2)^A, (n=1)^B 	 Decreased confidence (n=4)^A Feeling old (n=3)^A Feeling less attractive (n=1)^A Body image (n=1)^A Loss of femininity (n=1)^A Feeling inadequate (n=1)^A Feeling vulnerable (n=1)^A 	 Crying spells/tearful (n=2)^A Emotionally sensitive (n=2)^A Phobias (n=1)^A Physical functioning Ability to exercise (n=3)^A, (n=6)^B Reduced stamina (n=1)^A 		
"I wake up and I'm sweating. I can' the window'			ne fan, open			Activities of daily living Reluctance to leave house (n=11)⁸ 	Work/education Needing breaks (n=1)^A, (n=10)^B 	Cognitive functioning • Reduced concentration (n=5) ^A , (n=4) ^B		
				<i>h I would probably say that I have</i> " (AET participant)	more than	 Dressing/changing clothes (n=6)^A, (n=10)^B Household tasks (n=2)^A, (n=4)^B Eating/drinking (n=3)^B Driving (n=3)^B Clumsiness (n=2)^A 	 Reduced productivity (n=4)^A, (n=5)^B Mood while at work (n=1)^A, (n=3)^B Missed hours (n=2)^A 	 Poor memory (n=6)^A, (n=1*)^B Brain fog (n=1*)^A 	 literature review or during VMS qualitation interviews. Dark blue concepts were reported to be associated with postmenopause and All but no evidence was available on wheth they were related to VMS. A reported in literature review. B reported in VMS qualitative interview 	

> 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 narticinante

RESULTS

Ethnicity, n (%)				VMS (hot flashes) (n=24) ^A , (n=20) ^B	2	IMPACTS ON HRQOL		VMS COPING MECHANISMS
Non-Hispanic or Non-Latino Hispanic or Latino	5 (50.0%) 5 (50.0%)	8 (80.0%) 2 (20.0%)	13 (65.0%) 7 (35.0%)	ASSOCIATED KEY			Cool down (n=18)		
· · · · · · · · · · · · · · · · · · ·	5 (50.070)	2 (20.076)	7 (55.076)			S	leep	Social wellbeing	• Fan
Race, n (%)			10 (50 00()		Tiredness/fatigue (n=13) ^a , (n=18) ^b	 Night-time_awakenings (n=10)^A, (n=15)^B 	 Awakening unrested (n=4)^A 	 Disrupted social activities (n=6)^A, (n=14)^B 	Opening windows
White Black (African Amorican	5 (50.0%)	5 (50.0%)	10 (50.0%)	 Cold sweats/chills (n=4)^A, (n=18)^B 		 Difficulty falling asleep (n=7)^A, (n=11)^B Reduced sleep quality (n=7)^A, (n=6)^B 	 Needing more sleep/naps (n=4)^A, (n=2)^B Awakening early (n=2)^A 	 Quality of relationships (n=13)^A, (n=10)^B 	 Air conditioning Cold pack/wet cloth Removing bedding
Black/African American Other (Hispanic)	4 (40.0%) 1 (10.0%)	3 (30.0%) 2 (20.0%)	7 (35.0%) 3 (15.0%)	Additional signs					
/lenopausal status, n (%)	, , , , , , , , , , , , , , , , , , ,					 Reduced sleep quantity (n=8)^A, (n=5)^B Insomnia (n=8)^A, (n=2)^B 	 Light sleep (n=1)^A 		 Showering
Premenopausal	N/A	3 (30.0%)	3 (15.0%)	 Headache (n=9)^A, (n=7)^B Dissinger (n=2)^A (n=4)^B 	• Dry skin (n=5) ^A	 Insomma (n=o) , (n=z); 			 Diet adjustments (n=11)
Perimenopausal	N/A	2 (20.0%)	2 (10.0%)	 Dizziness (n=3)^A, (n=4)^B Weight gain (n=10)^A, (n=3)^B Nausea (n=9)^A, (n=3)^B Dehydrated (n=3)^B Increased heart rate (n=2)^B Pain (n=12)^A, (n=2)^B 	 Stiffness (n=4*)^A Hair loss (n=3) ^A Frequent urination/UTI (n=2)^A Vaginal itching (n=2)^A Osteoporosis (n=2)^A Itchy skin (n=2)^A Itchy skin (n=2*)^A Bloating (n=2*)^A Bloating (n=2*)^A Obstipation (n=1*)^A Flatulence (n=1*)^A Diarrhoea (n=1*)^A 	Emotional wellbeing			 Increased exercise (n=4) Napkins/towels for sweating (n=3)
Postmenopausal	10 (100%)	4 (40.0%)	14 (70.0%)			A Annu finitum (n. 1214 (n. 618	 Sense of self (n=7)^A 	 Lack of initiative listorant (s. 2)) 	 Supplements (n=2) Therapy (n=1) Taking breaks (n=1) Emotional coping (n=1) Concept classification n= Number of participants reported during VMS qualitative interview or number of articles reported in literature review. Orange concepts were associated with
Unknown	N/A	1 (10.0%)	1 (5.0%)			 Angry/irritated (n=12)^A, (n=8)^B Frustrated/impatient (n=5)^A, (n=8)^B Anxious/nervous/afraid (n=10)^A, (n=7)^B Embarrassed (n=3)^A, (n=7)^B Low mood/sad (n=11)^A, (n=5)^B Mood swings (n=8)^A, (n=4)^B Wanting to be alone (n=2)^A, (n=1)^B 	 Decreased confidence (n=4)^A Feeling old (n=3)^A Feeling less attractive (n=1)^A Body image (n=1)^A Loss of femininity (n=1)^A Feeling inadequate (n=1)^A Feeling vulnerable (n=1)^A 	 Lack of initiative/interest (n=3)^A Crying spells/tearful (n=2)^A Emotionally sensitive (n=2)^A Phobias (n=1)^A 	
uration 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%)	 Appetite changes (n=3)^A, (n=1*)^B Weak (n=3)^A, (n=1*)^B 				Physical functioning	
>10 years	0 (0%)	1 (10.0%)	1 (5.0%)	 Premonitory aura/sensation (n=1)^A Blurred vision (n=1*)^B Feeling shaky (n=1*)^B Light sensitivity (n=1*)^B 					
								 Ability to exercise (n=3)^A, (n=6)^B Reduced stamina (n=1)^A 	
"I wake up and I'm sweating. I can't sleep good. I have to turn the fan, open				 Arm edema (n=1*)^A 	Activities of daily living	Work/education	Cognitive functioning	VMS in the reviewed literature or VMS qualitative interviews.	
the window" "There's probably not a day that goe five, upv	es by that I do	on't have some			more than	 Reluctance to leave house (n=11)⁸ Dressing/changing clothes (n=6)^A, (n=10)⁸ Household tasks (n=2)^A, (n=4)⁵ Eating/drinking (n=3)⁸ Driving (n=3)⁸ Clumsiness (n=2)^A 	 Needing breaks (n=1)^A, (n=10)^B Reduced productivity (n=4)^A, (n=5)^B Mood while at work (n=1)^A, (n=3)^B Missed hours (n=2)^A 	 Reduced concentration (n=5)^A, (n=4)^B Poor memory (n=6)^A, (n=1*)^B Brain fog (n=1*)^A 	 * indicates concepts which were reported by participants receiving AET only in the literature review or during VMS qualitation interviews. Dark blue concepts were reported to be associated with postmenopause and AET but no evidence was available on whether they were related to VMS. A reported in literature review. B reported in VMS qualitative interviews.

Concept elicitation

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.



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









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To view the reference list

- 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 8b²⁰ and MENQOL¹⁷ 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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