

Psychometric Evaluation of the MENQOL Instrument in Women Experiencing Vasomotor Symptoms Associated with Menopause

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Supplementary Table S1. The other patient-reported outcome instruments included in this analysis

The Patient-Reported Outcomes Measurement Information System Sleep-Related Impairment – Short Form 8a (PROMIS SRI SF 8a) comprises eight items selected from the PROMIS SRI item bank. The form encompasses self-reported perceptions of alertness, sleepiness, and tiredness during usual waking hours, as well as perceived functional impairments during wakefulness that are associated with sleep problems or impaired alertness. The PROMIS SD SF 8b also includes eight items from the PROMIS SRI item bank to measure sleep disturbance across the severity continuum. Respondents were asked to record sleep disturbance during the previous 7 days. The total score for each PROMIS SRI SF measure was calculated by summing the items, and could be calculated only if all eight items were completed. Scores on both scales range between 8 and 40, with higher scores associated with more disturbed sleep.

For assessment of vasomotor symptom (VMS) episodes, participants recorded the number of VMS and the severity of each episode using an electronic daily diary. The severity of each episode was defined as mild (sensation of heat but no sweating), moderate (sensation of heat with sweating, but able to continue activity), or severe (sensation of heat and sweating causing cessation of activity) [1, 2].

On the Patient Global Impression of Severity Sleep Disturbance (PGI-S SD), respondents rated the overall severity of their current sleep disturbance on a four-point scale (0 = no problems; 3 = severe problems).

Changes in sleep disturbance and VMS were measured using the Patient Global Impression of Change Sleep Disturbance (PGI-C SD) and PGI-C VMS instruments, respectively. Respondents rated the overall change from baseline to Weeks 4 and 12 in their sleep disturbance and VMS on a seven-point scale (much worse = -3; much better = +3).

The EuroQoL 5-dimension 5-level (EQ-5D-5L) questionnaire measures mobility, self-care, usual activities, pain/discomfort, and anxiety/depression [3]. Respondents rated each item with one of five responses: no problems, slight problems, moderate problems, severe problems, and unable to/extreme problems. The EQ Visual Analog Scale (VAS) records overall self-rated health status on a vertical VAS from 0 (the worst health you can imagine) to 100 (the best health you can imagine).

The Work Productivity and Activity Impairment questionnaire specific to Vasomotor Symptoms (WPAI-VMS) consists of six items that examine impairments in work productivity and activity in the preceding 7 days as a result of VMS. Four domain scores are produced using the WPAI-VMS: absenteeism (percentage of work time missed because of VMS), presenteeism (percentage of impairment experienced while at work because of VMS), overall work productivity loss (measured by combining absenteeism and presenteeism to determine the total percentage of missed time), and activity impairment (percentage impairment in daily activities because of VMS). Outcomes are expressed as percentages, with higher numbers indicating greater impairment and less productivity.

In the present analysis, the PROMIS SRI SF 8a and 8b, VMS episodes, PGI-S SD, EQ VAS, and WPAI-VMS were used to assess convergent validity, while the PROMIS SRI SF 8a and 8b, VMS episodes, PGI-S SD, PGI-C SD, PGI-C VMS, and EQ VAS were used to assess sensitivity to change. Additionally, the PGI-S SD was used to assess known-groups validity, and the PGI-S SD and the PGI-C SD were used to derive the responder definition.

References

1. Guidance for industry. Estrogen and estrogen/progestin drug products to treat vasomotor symptoms and vulvar and vaginal atrophy symptoms — recommendations for clinical evaluation. Draft guidance. 2003. <https://www.fda.gov/media/71359/download>. Accessed 5 Feb 2024.
2. Guideline on clinical investigation of medicinal products for hormone replacement therapy of oestrogen deficiency symptoms in postmenopausal women. 2005. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-investigation-medicinal-products-hormone-replacement-therapy-oestrogen-deficiency_en.pdf. Accessed 5 Feb 2024.
3. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res. 2011;20:1727–36.

Supplementary Table S2. Categories anchor measure score responses at Weeks 4 and 12 – mean change

Anchor	Anchor category	Definition
PGI-C VMS at Weeks 4/12 – all categories	Much better	Score of +3 (“much better”)
	Moderately better	Score of +2 (“moderately better”)
	A little better	Score of +1 (“a little better”)
	No change	Score of 0 (“no change”)
	A little worse	Score of –1 (“a little worse”)
	Moderately worse	Score of –2 (“moderately worse”)
	Much worse	Score of –3 (“much worse”)
PGI-C VMS at Weeks 4/12 – collapsed categories 1	Much better or moderately better	Score of +3 or +2 (“much better” or “moderately better”)
	Moderately worse or much worse	Score of –2 or –3 (“moderately worse” or “much worse”)
PGI-C VMS at Weeks 4/12 – collapsed categories 2	Improvement	≥ 1-point increase (little, moderately, or much better levels)
	No change	0 points (no change)
	Worsening	≥ 1-point decrease (little, moderately, or much worse levels)

Response at Weeks 4 and 12 was analyzed for the PGI-C VMS anchor

PGI-C VMS Patient Global Impression of Change Vasomotor Symptoms

Supplementary Table S3. Categories for anchor measure score responses at Weeks 4 and 12 – ROC curve

Anchor	Anchor category	Definition
PGI-C VMS at weeks 4/12 – collapsed categories (ROC)	Responder	“Moderately better” or “much better” levels (i.e., score of +2 and +3)
	Non-responders	All other levels (i.e., score of +1, 0, -1, -2, and -3)

Response was analyzed at Weeks 4 and 12 for the PGI-C VMS anchor

PGI-C VMS Patient Global Impression of Change Vasomotor Symptoms, *ROC* receiver operating characteristic

Supplementary Table S4. MENQOL item and domain scores over time (FAS)

Mean (SD) score	Baseline (n = 1017)	Week 4 (n = 932)	Week 12 (n =865)
Item scores			
Item 1: hot flushes or flashes	6.57 (1.69)	4.85 (2.10)	4.53 (2.20)
Item 2: night sweats	6.58 (1.68)	4.84 (2.18)	4.46 (2.28)
Item 3: sweating	6.41 (1.80)	4.52 (2.31)	4.08 (2.31)
Item 4: dissatisfaction with personal life	3.20 (2.66)	2.33 (2.17)	2.22 (2.07)
Item 5: feeling anxious or nervous	3.80 (2.53)	2.90 (2.26)	2.82 (2.17)
Item 6: poor memory	3.25 (2.45)	2.60 (2.10)	2.58 (2.06)
Item 7: accomplishing less than used to	3.62 (2.53)	2.44 (2.09)	2.49 (2.13)
Item 8: feeling depressed, down or blue	2.89 (2.32)	2.24 (1.95)	2.29 (1.95)
Item 9: being impatient with other people	3.83 (2.41)	2.79 (2.14)	2.79 (2.14)
Item 10: feelings of wanting to be alone	2.97 (2.36)	2.34 (2.07)	2.41 (2.05)
Item 11: passing gas or gas pains	3.03 (2.36)	2.77 (2.20)	2.83 (2.22)
Item 12: aching in muscles and joints	4.12 (2.52)	3.31 (2.39)	3.39 (2.47)
Item 13: feeling tired or worn out	4.87 (2.32)	3.73 (2.31)	3.58 (2.31)
Item 14: difficulty sleeping	5.60 (2.34)	4.14 (2.43)	3.85 (2.48)
Item 15: aches in back of neck or head	3.88 (2.65)	3.06 (2.36)	2.95 (2.32)
Item 16: decrease in physical strength	3.67 (2.51)	2.61 (2.20)	2.64 (2.20)
Item 17: decrease in stamina	3.96 (2.45)	2.86 (2.24)	2.80 (2.22)
Item 18: lack of energy	4.41 (2.40)	3.22 (2.26)	3.25 (2.30)
Item 19: dry skin	4.02 (2.53)	3.34 (2.40)	3.31 (2.41)
Item 20: weight gain	3.48 (2.82)	2.66 (2.45)	2.81 (2.49)
Item 21: increased facial hair	2.13 (2.15)	1.59 (1.58)	1.70 (1.70)
Item 22: changes in appear/texture/tone of skin	2.90 (2.47)	2.00 (1.94)	2.11 (2.03)
Item 23: feeling bloated	3.31 (2.58)	2.53 (2.19)	2.66 (2.29)
Item 24: low backache	3.75 (2.63)	3.00 (2.38)	2.98 (2.39)
Item 25: frequent urination	3.30 (2.60)	2.60 (2.28)	2.65 (2.26)
Item 26: involuntary urination when laugh/cough	2.69 (2.36)	2.12 (1.99)	2.17 (2.05)
Item 27: decrease in sexual desire	3.78 (2.78)	2.85 (2.55)	2.91 (2.58)
Item 28: vaginal dryness	3.76 (2.77)	3.11 (2.53)	3.11 (2.54)
Item 29: avoiding intimacy	3.29 (2.80)	2.69 (2.50)	2.73 (2.52)
Domain scores			
Vasomotor	6.52 (1.49)	4.74 (1.98)	4.36 (2.06)
Psychosocial	3.37 (1.82)	2.52 (1.61)	2.51 (1.59)

Physical	3.69 (1.60)	2.85 (1.44)	2.85 (1.49)
Sexual	3.61 (2.40)	2.88 (2.21)	2.91 (2.22)
Overall score	4.30 (1.37)	3.25 (1.36)	3.16 (1.37)

Scores are presented as mean (standard deviation). Higher scores indicate greater impairment

FAS full analysis set, *MENQOL* Menopause Quality of Life Questionnaire

a)

[illegible]

b)

[illegible]

c)

Item	Item 21	Item 22	Item 23	Item 24	Item 25	Item 26	Item 27	Item 28	Item 29
Item 21: increased facial hair	–	0.64	0.52	0.37	0.43	0.34	0.37	0.31	0.35
Item 22: changes in appear/texture/tone of skin		–	0.57	0.36	0.37	0.31	0.47	0.39	0.44
Item 23: feeling bloated			–	0.49	0.46	0.36	0.46	0.30	0.43
Item 24: low backache				–	0.44	0.36	0.35	0.26	0.38
Item 25: frequent urination					–	0.50	0.34	0.31	0.33
Item 26: involuntary urination when laugh/cough						–	0.32	0.30	0.32
Item 27: decrease in sexual desire							–	0.71	0.84
MENQOL Sexual score									
Item 28: vaginal dryness								–	0.67
Item 29: avoiding intimacy									–

Polychoric correlation coefficients are shown. Shaded cells indicate item-to-item correlations < 0.40 within the MENQOL domain

MENQOL Menopause-Specific Quality of Life questionnaire

Supplementary Table S6. Anchor evaluation: correlations between MENQOL overall and domain scores and anchor change from baseline to Weeks 4 and 12

MENQOL score/Visit	PGI-S VMS change categories	
	n	r
Overall		
Week 4	929	0.48
Week 12	862	0.47
Vasomotor domain		
Week 4	929	0.60
Week 12	862	0.60
Psychosocial domain		
Week 4	929	0.30
Week 12	862	0.30
Physical domain		
Week 4	929	0.29
Week 12	862	0.28
Sexual domain		
Week 4	929	0.18
Week 12	862	0.18

Spearman correlations are shown.

MENQOL Menopause-Specific Quality of Life questionnaire, *PGI-C VMS*, Patient Global Impression of Severity Vasomotor Symptoms

Supplementary Table S7. ROC curve analysis of MENQOL overall and domain scores: responder vs non-responder

Timepoint	Anchor	AUC	Sensitivity	Specificity	Criterion
MENQOL overall score					
Baseline to Week 4	PGI-C VMS	0.73	0.64	0.73	-1.08
Baseline to Week 12	PGI-C VMS	0.75	0.71	0.70	-0.91
MENQOL Vasomotor score					
Baseline to Week 4	PGI-C VMS	0.80	0.71	0.76	-2.00
Baseline to Week 12	PGI-C VMS	0.81	0.73	0.74	-2.00
MENQOL Psychosocial score					
Baseline to Week 4	PGI-C VMS	0.65	0.61	0.63	-0.71
Baseline to Week 12	PGI-C VMS	0.66	0.60	0.64	-0.71
MENQOL Physical score					
Baseline to Week 4	PGI-C VMS	0.64	0.62	0.58	-0.69
Baseline to Week 12	PGI-C VMS	0.66	0.61	0.64	-0.69
MENQOL Sexual score					
Baseline to Week 4	PGI-C VMS	0.57	0.51	0.56	-0.33
Baseline to Week 12	PGI-C VMS	0.60	0.54	0.60	-0.33

For PGI-C VMS, responders were defined by 'moderately better' or 'much better' improvement, with all other levels defined as non-responders.

AUC area under the curve, PGI-C VMS Patient Global Impression of Change Vasomotor Symptoms, ROC receiver operating characteristic

Figure S1. Model code

```
proc calis data=pro2 covariance plots=pathdiagram method=ml modification
outtram=model2_menqol;
pathdiagram arrange=groupedflow diagram=STANDARD notitle noflag fitindex=[nobs srmsr
rmsea cfi] label=[FACTOR1=Overall FACTOR2=Vasomotor FACTOR3=Psychosocial
FACTOR5=Sexual menqphmn=Physical];
    lineqs
        MENQL01 = a1 * FACTOR2 + e1,
        MENQL02 = FACTOR2 + e2,
        MENQL03 = a3 * FACTOR2 + e3,

        MENQL04 = a4 * FACTOR3 + e4,
        MENQL05 = a5 * FACTOR3 + e5,
        MENQL06 = a6 * FACTOR3 + e6,
        MENQL07 = a7 * FACTOR3 + e7,
        MENQL08 = FACTOR3 + e8,
        MENQL09 = a9 * FACTOR3 + e9,
        MENQL10 = a10 * FACTOR3 + e10,

        MENQL27 = FACTOR5 + e11,
        MENQL28 = a12 * FACTOR5 + e12,
        MENQL29 = a13 * FACTOR5 + e13,

        FACTOR2 = a14 * FACTOR1 + e14,
        FACTOR3 = a15 * FACTOR1 + e15,
        menqphmn = a16 * FACTOR1 + e16,
        FACTOR5 = a17 * FACTOR1 + e17;
    variance
        FACTOR1 = 1,
        e1-e17 = ve1-ve17;
    var MENQL01-MENQL10 MENQL27-MENQL29 menqphmn;
run;
```

Figure S2. Confirmatory factor analysis of MENQOL overall score at baseline (second-order model)

