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ORIGINAL ARTICLE

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Transdermal estradiol spray in Nordic menopausal women: real-world patient outcomes

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ABSTRACT

Objective: This study aimed to evaluate the impact of transdermal estrogen therapy on health-related quality of life (HRQoL) and treatment tolerability in postmenopausal women in a real-world setting.

Method: A prospective, non-interventional study was conducted in Sweden and Finland. Participants used a spray delivering 1.53 mg of estradiol (E_2) per 90 µl dose. HRQoL (measured using the Menopause Rating Scale [MRS]), dosing patterns and treatment satisfaction were assessed through web-based questionnaires at baseline, week 6 and week 12. Mixed-model repeated-measures analysis was performed.

Results: Of 249 participants (mean age 52.1 years), 165 (66.3%) completed the 12-week follow-up. Most women (67.2%) used one or two sprays daily. The mean MRS total score was 17.8 at baseline, and decreased by 8.6 points at week 6 ($p = 0.012$) and 9.9 points by week 12 ($p < 0.0001$). Improvements were seen across all MRS domain scores (somatovegetative, psychological and urogenital), including hot flashes, sleep issues, depressive moods and sexual problems. Most participants reported satisfaction (78.8%), ease of use (95.2%) and willingness to recommend the spray to a friend (84.2%). No related adverse reactions were reported.

Conclusion: The E_2 spray improved HRQoL and was well tolerated. Flexible dosing, ease of use and real-world effectiveness support that the spray is a practical, user-friendly treatment for menopausal symptoms.

PLAIN LANGUAGE SUMMARY

In this study, 249 women in Sweden and Finland used a transdermal spray that delivers estradiol, a type of estrogen, through the skin. Participants completed online surveys at the start of the study and again at 6 and 12 weeks, using the Menopause Rating Scale to assess overall well-being.

Most women applied one to two sprays per day on one arm. Over the course of the study, they experienced substantial improvement. By week 12, the average symptom score had decreased by half, which was a clinically meaningful change. Symptoms such as hot flashes, night sweats, sleep disturbances, low mood and sexual problems improved over time. The spray was well tolerated, and most participants found it easy to use. Nearly 80% reported being satisfied with the treatment, and more than 84% said they would recommend it to a friend.

Overall, the estradiol spray effectively reduced menopausal symptoms and improved daily functioning for most participants. Its proven effectiveness, ease of use and flexible dosing make estradiol spray a practical option for day-to-day management of menopausal symptoms.

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KEYWORDS

Transdermal estradiol spray; menopausal hormone therapy; real-world evidence; quality of life; Menopause Rating Scale

Introduction

Menopause is linked to a wide range of physical and psychological symptoms, including vasomotor symptoms (VMS), sleep disturbances, mood swings and vaginal dryness, all of which can significantly reduce quality of life (QoL) [1]. Especially, VMS have been shown to affect daily activities and work performance [1–3]. In the Nordics, 11–14% of women reported experiencing moderate to severe VMS in a large cross-sectional survey involving 6383 postmenopausal women aged 40–65 years. Interestingly, 62% of these women were not taking any medication for their symptoms [4].

VMS can be effectively managed with menopausal hormone therapy (MHT). In fact, using MHT during the climacteric period has been linked to significant improvements in health-related quality of life (HRQoL) [1]. MHT can be taken orally, but transdermal delivery is also a viable option. Unlike oral medications, transdermal forms bypass first-pass metabolism in the liver, which results in a lower impact on hemostasis and a reduced risk of drug interactions [5,6]. This makes transdermal MHT a safer and more suitable alternative, especially for women with cardiovascular risk factors or gastrointestinal issues [1,7–10].

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The estradiol (E_2) transdermal spray is an approved treatment for alleviating menopausal symptoms. It is currently the only transdermal spray available for this purpose. The E_2 transdermal spray is absorbed through the skin after application, forming a reservoir in the stratum corneum of the skin epidermis from which E_2 is slowly released into the bloodstream, resulting in stable E_2 blood levels [11]. Phase III data from a randomized trial with 454 postmenopausal women in the USA showed a significant reduction in hot flash frequency across the one, two and three-spray dosing schedules [12].

The use of a transdermal E_2 spray is effective and well tolerated in healthy postmenopausal women, as seen in randomized clinical trials. However, real-world evidence is needed to show its everyday clinical effectiveness in the diversity of women encountered in routine clinical practice.

This study aims to address the lack of real-world effectiveness data in the Nordics, particularly Sweden and Finland.

Methods

Study design and population

This 12-week, prospective, non-interventional cohort study was conducted at 28 clinics in Sweden and 24 clinics in Finland. Women experiencing menopausal symptoms who sought treatment were recruited if they were not using the E_2 transdermal spray, had not received any other E_2 treatment in the past 2 months and had no contraindications for MHT. They agreed to start treatment with the E_2 transdermal spray independently of the study as part of their clinical care.

Participants applied one transdermal E_2 spray daily (one spray of 90 µl contains 1.53 mg E_2). Depending on their responses, women could adjust the dosage to two or three sprays daily, applying each spray to an adjacent, non-overlapping area on the inner forearm or, if necessary, the inner thigh according to the manufacturer's instructions. All participants were expected to have sufficient knowledge of either Swedish or Finnish. No in-person visits or direct contact with the clinic occurred during the study period, except for a visit when treatment with the transdermal E_2 spray started. All follow-up data were collected via web-based questionnaires completed by the participants at baseline, week 6 and week 12. Baseline questionnaires also gathered information on age (years), height (centimeters), weight (kilograms), smoking status (yes/no) and prior MHT treatments (including the use of progestin).

A total of 252 eligible women enrolled and consented to participate in the study between September 2018 and June 2020, with 249 participants ultimately included. The week 6 questionnaire was completed by 196 women (78.7%) and the week 12 questionnaire by 165 women (66.3%). At the respective time points, 186 (74.7%) and 154 (61.8%) women were still on treatment. The higher numbers of completed questionnaires compared with participants on treatment at weeks 6 and 12 are explained by participants who had discontinued treatment before these time points but nevertheless completed the questionnaires; their data were included based on their reported experience during the on-treatment period. Overall, questionnaire response rates were similar across both countries (at week 12, 65.8% for Sweden and 67.0% for Finland).

Outcome measures

Menopause Rating Scale

The primary outcome was HRQoL, assessed using the validated Menopause Rating Scale (MRS), a self-administered severity assessment of 11 symptoms grouped into three dimensions: somatovegetative (hot flashes and sweating, heart discomfort, sleep disturbances, and joint and muscular pain), psychological (depressive mood, irritability, anxiety, and physical or mental exhaustion) and urogenital (sexual problems, bladder problems and vaginal dryness). Severity ratings range from 'no symptom' (0 points) to 'mild' (1 point), 'moderate' (2 points), 'severe' (3 points) and 'very severe' (4 points), with a total score range of 0 – 44 points. Lower scores indicated better QoL, and a change of 5 points or more was considered clinically relevant [13].

Self-assessment of menopausal symptoms

The questionnaire also included the statements 'Compared to pretreatment state, my menopausal symptoms are', which was assessed using a 7-point Likert scale from 'very much improved' to 'very much worse', and 'Presently, my perceived menopausal symptoms negatively impact my quality of life' that was assessed using a 5-point Likert scale from 'strongly disagree' to 'strongly agree'.

Both the MRS and the self-assessment of menopausal symptoms were included in the baseline, week 6 and week 12 questionnaires.

Satisfaction

In addition, at week 12, treatment satisfaction/usage satisfaction was assessed via collecting feedback for the statements 'I am satisfied with the treatment', 'I found the spay easy to use' and 'I would recommend the spray to a friend', using a 5-point Likert scale from 'strongly disagree' to 'strongly agree'. Furthermore, the subjects were asked to record the use of any local/vaginal estrogen treatments.

Safety

Adverse drug reactions related to the use of the transdermal spray were collected to assess safety.

Statistical analysis

Changes in the MRS total score and dimension scores at week 6 and week 12 were treated as continuous variables. Descriptive statistics included the mean, standard deviation (SD), median, minimum and maximum. The quantitative variables, and MRS total scores, were used in subgroup analyses by age (≤50 years, >50 years), body mass index (BMI: <25 kg/m^2, 25 – 29 kg/m^2, ≥30 kg/m^2) and baseline MRS score (below/above median). Changes in HRQoL, as measured by the MRS

total score and domain scores at baseline, week 6 and week 12, were analyzed using a mixed model for repeated measures. The model included the covariates of MRS total score at baseline, visit, country, number of sprays used at week 6 and week 12, age (by subgroup), BMI (by subgroup) and smoking status (yes/no) to control for potential confounding factors. An unstructured covariance matrix was used to model the within-subject error.

Post hoc, the frequencies of participants in each of the MRS severity categories were compared with baseline using a chi-square test.

Based on prior data showing a mean change of −8.66 (SD: ±6.88) in the MRS total score, a sample size of approximately 170 participants was estimated to provide 90% power to detect a mean change of at least −5 points from baseline to week 12 (one-sided test, $\alpha = 0.05$) [14].

For the perceived symptom improvement, question responses were coded from +3 (very much improved) to −3 (very much worse). Both were analyzed using the described mixed-effects model for repeated measures. For the QoL impact question, responses were coded from +2 (strongly disagree) to −2 (strongly agree). Treatment satisfaction was analyzed descriptively using frequency distributions. Safety was analyzed descriptively by country. All available data were used in the statistical analysis. Participants who withdrew before the last planned week 12 were included in the analyses up to the time of discontinuation. No imputations were performed, and no last observation carried forward was carried out. Partial non-responses did not occur, as the questionnaires could not be submitted unless at least one question was answered.

p-Values of <0.05 were considered statistically significant. Statistical analyses were performed using the SAS System for Windows, version 9.4 (SAS Institute Inc., Cary, NC, USA). Post hoc analyses were performed using Prism 10 for Windows (version 10.5.0; GraphPad Software L.L.C).

Table 1. Demographic and clinical characteristics.

Characteristic	*Total* (n = *249*)	*Finland* (n = *88*)	*Sweden* (n = *161*)
Age (years)			
Mean (SD)	52.1 (4.31)	53 (3.41)	51.6 (4.63)
Median	52	53	51
Minimum, maximum	36, 73	43, 64	36, 73
BMI (kg/m^2)			
Mean (SD)	26.1 (4.48)	26.7 (4.87)	25.7 (4.23)
Median	25.4	25.7	25.3
Minimum, maximum	15.1, 40.2	19.6, 39.3	15.1, 40.2
Smoker (yes), *n* (%)	18 (7.2%)	8 (9.1%)	10 (6.2%)
Prior use of MHT (yes), *n* (%)	45 (18.1%)	15 (17.0%)	30 (18.6%)
Use of a progestin (yes), *n* (%)	123 (49.4%)	42 (47.7%)	81 (50.3%)
Hormone intrauterine device	65 (26.1%)	28 (31.8%)	37 (23.0%)
Oral	58 (23.3%)	14 (15.9%)	44 (27.3%)
MRS total score below the median at baseline, *n* (%)	117 (47.0%)	52 (59.1%)	65 (40.4%)

BMI, body mass index; MHT, menopausal hormone therapy; MRS, menopause rating scale; SD, standard deviation.

Results

Demographic and clinical characteristics

Participant characteristics are summarized in Table 1. The average age at enrollment was 52.1 years (median 52 years), and the mean BMI was 26.1 kg/m^2 (median 25.4 kg/m^2). Almost one-fifth reported prior use of MHT. Overall, participant characteristics were consistent across countries. At baseline, 96.8% of the participants agreed or strongly agreed that their perceived menopausal symptoms had a negative impact on their QoL.

Quality of life as measured by the Menopause Rating Scale

Overall, the mean baseline total MRS score was 17.8 (SD: 6.4). The mean change from baseline was −8.6 (SD: 6.0) at week 6 ($p = 0.012$) and −9.9 (SD: 5.8) at week 12 ($p < 0.0001$) (Figure 1). At week 12, the mean change from baseline was more pronounced compared to week 6 ($p < 0.0001$).

Baseline mean MRS scores were 18.6 (SD: 6.5) in Sweden and 16.1 (SD: 5.8) in Finland. In Sweden, mean changes from baseline were −8.7 (SD: 6.3) at week 6 and −10.4 (*SD*: 5.9) at week 12; the corresponding changes in Finland were −8.2 (SD: 5.1) and −8.9 (*SD*: 5.5) at week 6 and 12, respectively (Figure 1)

Improvements were observed in all MRS domains: somatovegetative symptoms decreased by −3.6 at week 6 and −4.2 at week 12; psychological symptoms by −3.4 at week 6 and −3.7 at week 12; and urogenital symptoms by −1.6 and −1.9, respectively ($p < 0.0001$).

The proportion of participants reporting very severe, severe and moderate individual symptoms decreased, while the proportion increased for mild and no symptoms across all MRS items at weeks 6 and 12 (Figure 2). This appeared to be most pronounced for sleep problems, hot flushes/sweating, depressive mood, sexual problems, and joint and muscular discomfort, based on a cut-off of >20% in total percentage of participants experiencing very severe and severe symptoms (Supplemental Table 1).

Subgroup analyses demonstrated that the improvements in total MRS and MRS domain scores were consistent across all three dosing regimens (one spray, two sprays or three sprays), across all age groups, across BMI subsets and among those using an estrogen combined with progestin. The least square (LS) mean improvement was −8.75 for participants with a baseline MRS score at or above the median, and −7.88 for those with a baseline score below the median (Supplemental Table 2).

Self-assessment of menopausal symptoms

Mean improvements in perceived menopausal symptoms and in their impact on QoL were observed at week 6 ($p < 0.0001$) and week 12 ($p < 0.0001$) (Table 2).

At week 6, 67.2% of the participants reported that their perceived symptoms were much or very much improved. Percentages for no change, minimally worse and much worse

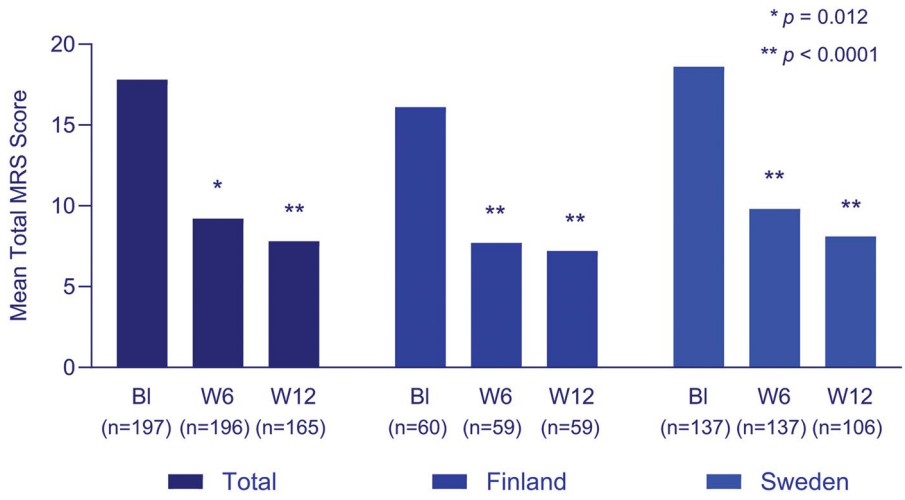

Figure 1. Menopause Rating Scale (MRS) total score. Changes from baseline were analyzed via a mixed model for repeated measures, which included the following covariates: MRS total score at baseline, visit, country, number of sprays used at week 6 and week 12, age (by subgroup), body mass index (BMI) (by subgroup) and smoking status (yes/no). BL, baseline; W6, week 6; W12, week 12.

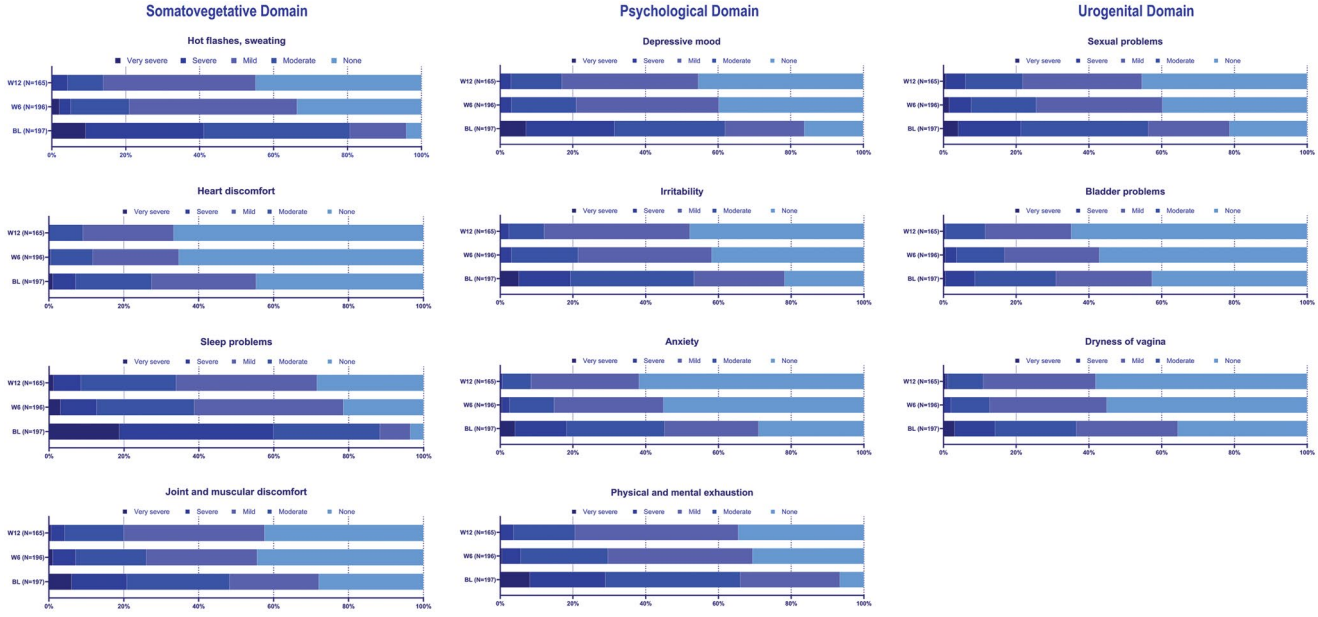

Figure 2. Percentage of participants in each Menopause Rating Scale (MRS) severity class, by domain and symptom. BL, baseline; W6, week 6; W12, week 12.

Table 2. Participant-reported changes in the impact of negative symptoms on their perceived menopausal symptoms and quality of life.

		Change from baseline	
Question	*Baseline*	*Week 6* (n = *196*)	*Week 12* (n = *165*)
'Compared to the pretreatment state, my menopausal symptoms are …'[a]			
Mean (SD)	–	1.9 (1.04)	2.1 (1.03)
Median	–	2	2
Minimum, maximum	–	−2, 3	−2, 3
p-Value		<0.0001	<0.0001
'Presently, my menopausal symptoms negatively impact my quality of life'[b]			
Mean (SD)	−1.5 (0.57)	1.7 (1.17)	2 (1.13)
Median	−1	2	2
Minimum, maximum	−2, 1	−1, 4	−1, 4
p-Value		<0.0001	<0.0001

[a]For the symptom improvement question, the responses were scored from +3 (very much improved) to −3 (very much worse); baseline was set at 0.
[b]For the question about the impact of perceived symptoms on quality of life (QoL), responses were coded from +2 (strongly disagree) to −2 (strongly agree).
Changes from baseline were analyzed via mixed-model repeated-measures analysis, which included the following covariates: Menopause Rating Scale (MRS) total score at baseline, visit, country, number of sprays used at week 6 and week 12, age (by subgroup), body mass index (BMI) (by subgroup) and smoking status (yes/no). SD, standard deviation

Figure 3. Patient-reported improvement of their perceived menopausal symptoms (A) and their impact on quality of life (B). For the impact of perceived symptoms on quality of life (QoL) question ('Presently, my menopausal symptoms negatively impact my quality of life'), responses were coded from +2 (strongly disagree) to −2 (strongly agree). For the symptom improvement question ('Compared to the pretreatment state, my menopausal symptoms are …'), responses were scored from +3 (very much improved) to −3 (very much worse); baseline was set at 0. Fin, Finland; Swe, Sweden.

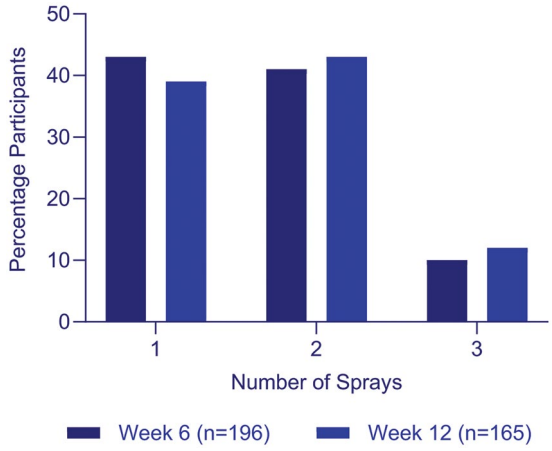

Figure 4. Percentage of participants using one, two or three sprays at week 6 and week 12. Of the participants, 5.1% and 6.7% reported using zero sprays or that they stopped treatment in weeks 6 and 12, respectively.

were 4.1%, 1.5% and 1.5%, respectively (Figure 3). At week 12, these percentages continued to improve, increasing by approximately 10%. Percentages for no change, minimally worse and much worse were 4.9%, 0.6% and 1.2%, respectively (Figure 3).

The proportion of participants who strongly agreed that their menopausal symptoms negatively affected their QoL decreased from 48.2% at baseline to 5.6% at week 6 (Figure 3). For those who agreed, the proportions declined from 49.8% to 25.0%. By week 12, the proportions further dropped to 2.4% and 17.0%, respectively (Figure 3).

Satisfaction

Satisfaction rates were high: 78.8% of the participants agreed or strongly agreed that they were satisfied with the treatment, and 95.2% agreed or strongly agreed that the E_2 transdermal spray was easy to use. Overall, 84.2% agreed or strongly agreed that they would recommend the spray to a friend.

Number of daily uses of estradiol transdermal sprays

At weeks 6 and 12, more than 80% of participants reported using one or two E_2 transdermal sprays daily (Figure 4). The proportions of participants applying three sprays daily were slightly higher in Sweden compared to Finland (12.4% vs. 5.1% and 16.0% vs. 3.4%, respectively, at weeks 6 and 12).

Safety

There were no reports of adverse events possibly related to use of the E_2 transdermal spray.

Discussion

The results of this observational study revealed that use of the E_2 transdermal spray led to a reduction in a broad spectrum of menopause-associated symptoms, such as hot flushes, night sweats, sleep problems, depressive mood and sexual problems, and subsequently improved overall QoL in postmenopausal participants. The symptom improvements were consistent across all age and BMI groups. Participants with higher baseline MRS scores showed greater absolute reductions in week 12, 3 months after treatment initiation, which aligns with the knowledge that those with severe symptoms derive the greatest benefit from MHT. Satisfaction rates were high, with more than 90% of participants finding the E_2 transdermal spray easy to use, suggesting that this

treatment approach is a practical, simple, convenient and possible alternative to oral estrogens.

The real-world evidence reported herein is well aligned with the results from the large phase III clinical trial and other published observational studies in the field [11,12,15–17]. In the phase III trial, use of the transdermal E_2 spray reduced hot flushes by 74–85% over 12 weeks [12], which is comparable to the symptom relief observed in the present study. Fait et al. further confirmed the long-term benefits of using the E_2 transdermal spray in a 24-week observational study, reporting a 66.2% overall reduction in MRS scores, with the most pronounced improvements found in VMS, heart discomfort and sexual problems [16]. Furthermore, a similar, 52-week real-world observational study conducted in Germany showed that 81.4% of the participants experienced significant relief from hot flashes and reported high overall satisfaction (73%) [15].

Real-world data provide crucial insights into patient adherence and satisfaction. Despite similar efficacy, real-world adherence is often lower due to factors such as treatment accessibility, lifestyle preferences and physician counseling. The observed adherence in the present study suggests that the E_2 transdermal spray is a well-accepted, practical option among Nordic women, complementing findings from structured clinical trials. These results are further supported by the outcome from a prospective, multicenter observational study in Portugal, which reported high user satisfaction (79.5% at 3 months and 82% at 6 months) in addition to significant symptom relief [17]. Furthermore, in that study, 90% of women found that the spray was easy to use, and 75% intended to continue treatment, highlighting strong adherence [17].

A potential limitation of the present study is the use of fully digital, personal, contact-free, self-administered questionnaires, which may have influenced overall engagement. Similar web-based patient-reported outcome studies have reported a wide range of response rates, typically between 60% and 80%, with lower rates in longer studies [18–20]. These benchmarks suggest that the adherence seen in the present study aligns with expectations for remote, real-world designs. Future studies may benefit from implementing automated reminders or offering optional clinic touchpoints to further enhance participant engagement and data completeness [21]. Nevertheless, the study yielded valuable Nordic region-specific real-world evidence beyond a controlled trial setting.

Overall, the findings of this study reinforce the role of the transdermal E_2 spray as a highly effective and well-tolerated treatment for menopausal symptoms. Real-world data complement controlled trial findings, showing that the use of the E_2 spray provides consistent, broad-spectrum symptom relief and high patient satisfaction. Furthermore, the findings of this study not only contribute to the understanding of the effectiveness of the transdermal E_2 spray but also to the broader need for better information dissemination among healthcare professionals and patients. As highlighted in a recent Swedish study, many women feel inadequately prepared for the menopausal transition and experience difficulties navigating healthcare options [22]. The real-world evidence presented herein could help support clinicians in providing clear guidance and information on accessible treatment options, ultimately addressing a known gap in menopausal care [23].

Conclusion

The E_2 transdermal spray improved HRQoL and was well tolerated. Flexible dosing options, convenient application and real-world effectiveness support its use as a practical treatment for menopausal symptoms.

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Ethical approval

The study was conducted in accordance with the Declaration of Helsinki and applicable local regulations. Ethics Committee approvals were obtained from The Swedish Ethical Review Authority (2018/1431–31/1).

Disclosure statement

P.P.-K. received travel and accommodation support from Gedeon Richter for the EMAS congress in Valencia 2025. M.L. is an employee of Gedeon Richter Nordics AB, Sweden. A.L.H. is a consultant for Astellas and Campus Pharma; and has received honoraria for lectures, presentations or educational events from Exeltis, Bayer Healthcare and Gedeon Richter, as well as research grants from Besins Health Care and Avia Pharma.

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Data availability statement

The data supporting the study findings are available from the corresponding author upon reasonable request.

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