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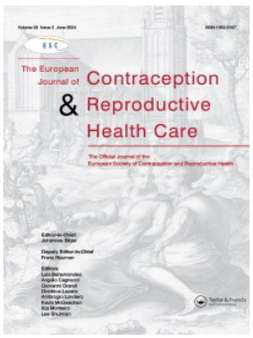

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RESEARCH ARTICLE

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Effects of E4/DRSP on self-reported physical and emotional premenstrual and menstrual symptoms: data from the phase 3 clinical trial in Europe and Russia

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ABSTRACT

Purpose: To describe the effects of estetrol (E4) 15 mg/drospirenone (DRSP) 3 mg on physical and emotional premenstrual and menstrual symptoms.

Materials and Methods: We used Menstrual Distress Questionnaire (MDQ) data from a phase-3 trial (NCT02817828) in Europe and Russia with participants (18 – 50 years) using E4/DRSP for up to 13 cycles. We assessed mean changes in MDQ-*t*-scores from baseline to end of treatment in premenstrual (4 days before most recent flow) and menstrual (most recent flow) scores for 4 MDQ domains in starters and switchers (use of hormonal contraception in prior 3 months) and performed a shift analysis on individual symptoms within each domain.

Results: Of 1,553 treated participants, 1,398(90.0%), including 531(38%) starters, completed both MDQs. Starters reported improvements for premenstrual Pain (–1.4), Water Retention (–3.3) and Negative Affect (–2.5); and for menstrual Pain (–3.5), Water Retention (–3.4), and Negative Affect (–2.7) (all $p<0.01$). For switchers, no changes were significant except an increase in premenstrual (+1.0, $p=0.02$) and menstrual (+1.5, $p=0.003$) Water Retention. We observed a change in symptom intensity in >40% of participants for Cramps, Backache and Fatigue (domain Pain), Painful or Tender Breast and Swelling (domain Water Retention) and Mood Swings and Irritability (domain Negative Affect).

Conclusion: E4/DRSP starters experienced significant improvements in the domains Pain, Water Retention and Negative Affect particularly benefiting those with more severe baseline symptoms. Switchers showed minimal changes.

SHORT CONDENSATION

A phase 3 study in Europe and Russia showed that Estetrol/Drospirenone, a new combined oral contraceptive, significantly improved the MDQ scores for domains Pain, Water Retention and Negative Affect in women starting COC use, while switchers showed minimal changes.

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Estetrol; E4; E4/drsp; combined oral hormone contraception; menstrual distress questionnaire

Introduction

Menstruation-related symptoms have an important impact on user preferences for contraceptives [1]. When considering method choices, users incorporate information on contraceptive reliability, efficacy, and ease of use along with effects that can impact quality of life such as irregular bleeding, uterine cramping, breast tenderness, mood alterations, anxiety, water retention, concentration and headache [1–3].

Estetrol (E4) is a natural oestrogen marketed first for clinical use in a combined oral contraceptive containing E4 15 mg and drospirenone (DRSP) 3 mg. E4 is produced by the human foetal liver during pregnancy and synthesised from a plant source for clinical use. E4 displays selective tissue activity distinct from other natural and synthetic oestrogens [4]; as such, its clinical effects may be different compared to other oestrogen-containing contraceptives.

In Phase 2 clinical trials, E4/DRSP user acceptability, well-being and treatment satisfaction were compared with E4/LNG over 6 cycles using a self-reported Subject Satisfaction and Health-Related Questionnaire [5]. E4 15 mg/DRSP 3 mg, compared to E4 15 mg/LNG 150 mcg, was associated with higher user acceptability (study

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completion 72/79 (91.1%) vs 60/80 (80.0%), $p = 0.048$) and satisfaction at cycle 6 (57/78 (73.1%) vs 38/75 (50.6%), $p < 0.001$). Well-being was significantly better with E4/DRSP compared to E4/LNG (odds ratio 2.00 [95% confidence intervals 1.13- 3.53]). These findings suggest a benefit of E4/DSRP over E4/LNG.

In two Phase 3 clinical trials, E4/DRSP showed high contraceptive efficacy, a predictable bleeding pattern, and a favourable safety and tolerability profile [6,7]. The studies included a longitudinal evaluation of bothersome menstrual symptoms using the Menstrual Distress Questionnaire (MDQ). The MDQ is a self-reported standard validated instrument for measuring cyclical perimenstrual symptoms and comprised of 46 items clustered in 8 domains: 'Pain', 'Water Retention', 'Negative Affect', 'Impaired Concentration', 'Autonomic Reactions', 'Behaviour Change', 'Arousal', and 'Control' (Supplementary Table 1) [8]. In this planned secondary analysis, we present the MDQ results for the first 4 domains on physical and emotional premenstrual and menstrual symptoms from the E4/DRSP Phase 3 trial conducted in Europe and Russia.

Materials and methods

Trial design

The E4/DRSP Phase 3 trial in Europe and Russia was a multicentre, open-label, single arm study conducted from June 2016 to April 2018; the details of the study entry criteria and study visit schedule have previously been described (NCT02817828) [6]. Briefly, the trial included healthy, heterosexually active, pre-menopausal participants aged 18–50 years with a body mass index (BMI) ≤35 kg/m^2 and a history of regular menstrual cycles (21–35 days) when not using hormones. We included participants who had used oral, transdermal, vaginal, implantable, and intrauterine hormones within the 3 months before enrolment (switchers) and those who had not (starters). Participants received E4 15 mg DRSP 3 mg in a blister pack containing 24 active and 4 inactive tablets to be taken once daily for up to 13 cycles. Enrolled participants had scheduled follow-up evaluations at Cycles 2, 4, 7, and 10 and within 3 weeks of completing Cycle 13. Participants completed a baseline MDQ on or before the first day of E4/DRSP intake and at end of treatment (EoT) from Day 7–14 of Cycle 13 or at an early termination visit. MDQs in local language were used with validated translations except for the Polish translation. Participants rated symptoms occurring during the premenstrual (4 days before most recent flow), menstrual (most recent flow) and intermenstrual (the remainder of the cycle) phases. Items were scored on a 5-point scale ranging from 0 (no experience of symptoms) to 4 (symptoms are present, severe) for the 46 items/symptoms in the eight MDQ domains (Supplementary Table 1).

Analysis

For this analysis, we included all participants who received at least one dose of E4/DRSP and completed both a baseline and EoT MDQ. For each of the two menstrual phases, we excluded a domain score for an individual participant if the score for more than 2 domain items was missing [8]. When a score for one domain item was missing, we calculated the mean score of the remaining items and added it to the total raw score [9]. We calculated the domain raw scores (sum of item scores within each domain) (Supplementary Table 2) were rounded to the nearest whole number and converted to *t*-scores using the conversion tables from the MDQ-C manual [9]. This conversion allows a comparison of MDQ results between cycles, across cycle phases, and between participants [9].

We focused this evaluation on the 4 domains related to the menstrual symptoms previously demonstrated to be the most bothersome [10]: the physical domains of pain (6 items) and water retention (4 items) and the emotional domains of negative affect (8 items) and impaired concentration (8 items). The domains 'Behaviour Change,' 'Autonomic Reactions', 'Arousal', and 'Control' contain questions unrelated to the most bothersome menstrual symptoms. Because bothersome symptoms are typically not prevalent during the intermenstrual phase [8,9], we only evaluated outcomes in the premenstrual and menstrual phases.

We calculated MDQ domain *t*-scores at baseline and EoT for all participants and stratified by starters and switchers. The distribution of the change from baseline *t*-scores approximately followed a normal distribution. We compared mean EoT domain *t*-scores versus baseline using a two-sided paired t-test with α set at 0.05. We evaluated the proportion of observations that were outliers (more than 2 standard deviations larger than the mean) and evaluated outcomes with and without the outliers. We also evaluated outcomes with and without data obtained before Cycle 9 to assess the effect of early discontinuation.

We performed a shift analysis on the individual symptoms within each domain by calculating the proportion of participants shifting between intensity categories (severe, strong, moderate, mild or none) at baseline and EoT. We selected the items with at least 10% of participants with severe or strong complaints at baseline and a change in intensity in at least 40% of participants to create shift analysis figures. For the shift analyses, we defined significant improvement as a more than 10% difference between improvement rate and deterioration rate.

We used SAS® software (version 9.4) for Windows® to perform statistical analyses and considered a $p < 0.05$ as significant.

Results

Of the 1,553 participants who started study treatment, 1,398 (90.0%) completed both a baseline and EoT MDQ and are included in this analysis. Participants completed most EoT assessments in Cycle 9 – 13 ($n = 1,254$ [89.7%]), with 91 (6.5%) in Cycle 5 – 8, and 53 (3.8%) in Cycle 1 – 4 (Supplemental Figure 1). Demographics and characteristics for the analysis population are presented in Table 1.

The proportion of outliers was less than 5% for all domains and inclusion of their MDQ scores did not modify the overall results. Including the 10.3% of EoT MDQ scores obtained before Cycle 9 did not significantly modify the overall results (data not shown); therefore, we included the MDQ scores of all participants.

MDQ t-scores

T-scores for the 4 main MDQ domains for all participants are displayed in Table 2. Mean *t*-scores decreased significantly from baseline to EoT for menstrual 'Pain' (-1.4), and premenstrual and menstrual 'Negative Affect' (-0.7 and −1.1, respectively). Raw scores for all domains and *t*-scores for the other 4 MDQ domains are provided in Supplemental Tables 2 and 3, respectively.

T-scores for starters and switchers are presented in Table 3 and Figure 1. Overall, in the premenstrual and menstrual phases, numerically mean *t*-scores at baseline were higher for starters than for switchers for all domains. The mean *t*-scores for starters ($n = 531$) decreased significantly from baseline to EoT for premenstrual and menstrual 'Pain' (-1.4 and −3.5; respectively), 'Water Retention' (-3.3 and −3.4, respectively), and 'Negative Affect' (-2.5 and −2.7, respectively). For switchers ($n = 867$), *t*-scores increased significantly for premenstrual and menstrual 'Water Retention' (+1.1 and +1.5, respectively).

Table 1. Demographic characteristics of participants who completed the MDQ at baseline and at end of treatment in the Europe/russia phase 3 trial with E4/DRSP ($N = 1398$).

Characteristic	*n* (%) or mean ± standard deviation
Age (years)	27.2 ± 6.9
18 − 25	700 (50.1)
26–35	511 (36.6)
36–50	187 (13.4)
BMI (kg/m^2)	23.0 ± 3.5
< 25	1,073 (76.8)
25.0 to 29.9	242 (17.3)
≥ 30	83 (5.9)
Race	
Asian	9 (0.6)
Black	3 (0.2)
Other[a]	3 (0.2)
White	1,383 (98.9)
Smoking Status	
Former Smoker	62 (4.4)
Never Smoker	1,117 (79.9)
Current Smoker	219 (15.7)
Hormonal contraceptive use	
Starters[b]	531 (38.0)
Switchers[c]	867 (62.0)
Age (years) by past contraceptive use	
Starters	27.8 ± 7.1
Switchers	26.9 ± 6.8
BMI (kg/m^2) by past contraceptive use	
Starters	23.0 ± 3.7
Switchers	23.0 ± 3.3

BMI: body mass index; DRSP: drospirenone; E4: estetrol; MDQ: menstruation distress questionnaire; n: number.
[a]Includes America Indian or Alaska Native, Native Hawaiian or other Pacific Islanders and Other.
[b]No past hormonal contraceptive use or use >3 months before initiating study drug.
[c]Past hormonal contraceptive use within 3 months before initiating study drug.

MDQ - shift analysis

Seven of the total 26 symptoms had at least 10% of participants with severe or strong symptoms at baseline and showed changes in intensity of more than 40% of participants in either menstrual or premenstrual symptoms among switchers or starters. These symptoms were Cramps, Backache and Fatigue in the domain 'Pain', Painful or tender breasts and Swelling in the domain 'Water retention', and Mood swings and Irritability in the domain 'Negative affect' (Table 4). We observed changes primarily in starters, who reported notable improvements (more than 10% difference between participants improving versus worsening) for premenstrual Painful or tender breast, Swelling, Mood swings and Irritability and for menstrual Cramps, Backache, Painful or tender breasts, Swelling, Mood swings and Irritability (Table 4). The shifts were more pronounced (skipping two or more intensity levels) for those reporting improvement compared to those reporting worsening (Figures 2–4 and Supplemental Figures 2–5). These patterns were observed in both premenstrual and menstrual symptoms, as well as for starters and switchers, although improvement was less prominent for switchers compared to starters.

In the group of switchers, the percentage of participants with strong or severe symptoms at baseline was lower compared to starters, except for Headache (Table 4). Notably menstrual Headache showed more improvement in switchers compared to starters.

More detailed information on the actual shifts per baseline intensity score for the 3 symptoms with changes in over 50% of participants are provided in Figures 2–4 (Painful or tender breasts, Mood swings and Irritability) and in supplemental Figures 2–5 for symptoms with changes in 40–50% of participants (Cramps, Backpain, Fatigue and Swelling).

Discussion

Findings and interpretation

In this analysis, we used MDQ data from almost 1,400 healthy participants in Europe and Russia who used E4/DRSP for up to 13 months and assessed changes in premenstrual and menstrual scores for the physical and emotional MDQ domains of 'Pain', 'Negative Affect', 'Impaired Concentration' and 'Water Retention'. Several studies have demonstrated that these domains are the most severely affected by menstruation and most directly impact health-related quality of

Table 2. Mean baseline, EoT and change from baseline for menstrual and premenstrual MDQ *t*-scores in the Europe/russia phase 3 trial with E4/DRSP.

Domain	Phase	Score range	N[a]	Baseline	EoT	CfB	*p*-value[b]
Pain	Premenstrual	35-125	1,395	45.0 ± 11.1	44.7 ± 11.6	−0.2 ± 11.1	0.45
	Menstrual	31-120	1,394	45.2 ± 13.5	43.8 ± 13.8	−1.4 ± 13.3	<0.0001
Water retention	Premenstrual	32-120	1,395	44.0 ± 13.3	43.4 ± 13.4	−0.6 ± 14.2	0.12
	Menstrual	32-126	1,394	44.4 ± 14.1	44.0 ± 14.8	−0.3 ± 15.2	0.40
Impaired concentration	Premenstrual	40-157	1,394	45.4 ± 10.4	45.3 ± 10.5	−0.1 ± 10.7	0.76
	Menstrual	39-159	1,393	44.7 ± 10.5	44.8 ± 11.6	0.1 ± 11.5	0.69
Negative Affect	Premenstrual	34-103	1,395	43.4 ± 11.8	42.7 ± 11.8	−0.7 ± 11.5	0.03
	Menstrual	33-109	1,394	43.6 ± 12.9	42.5 ± 13.1	−1.1 ± 13.2	0.002

Data presented as mean ± standard deviation.
[a]Only includes participants who completed the MDQ at baseline and at end of treatment.
[b]Two-sided paired t-test with α set at 0.05.
CfB: change from baseline; DRSP: drospirenone; E4: estetrol; EoT: end of treatment; MDQ: menstruation distress questionnaire; *N*: number.

Table 3. Mean baseline, EoT and change from baseline for premenstrual and menstrual MDQ *t*-scores in the Europe/russia phase 3 trial with E4/DRSP - starters and switchers.

Starters[a] ($n=531$)							
Domain	Phase	Score range	n[b]	Baseline	EoT	CfB	*p*-value[c]
Pain	Premenstrual	35-125	530	45.5 ± 12.2	44.1 ± 11.8	−1.4 ± 11.3	0.0045
	Menstrual	31-120	530	46.2 ± 15.0	42.7 ± 14.1	−3.5 ± 13.0	<0.0001
Water retention	Premenstrual	32-120	531	46.8 ± 15.5	43.4 ± 13.9	−3.3 ± 14.8	<0.0001
	Menstrual	32-126	530	46.9 ± 15.8	43.5 ± 15.1	−3.4 ± 15.0	<0.0001
Impaired concentration	Premenstrual	40-157	530	46.5 ± 11.9	45.6 ± 11.5	−0.9 ± 11.5	0.08
	Menstrual	39-159	530	46.1 ± 11.8	45.6 ± 13.0	−0.5 ± 12.5	0.33
Negative Affect	Premenstrual	34-103	530	45.3 ± 13.5	42.8 ± 12.4	−2.5 ± 12.2	<0.0001
	Menstrual	33-109	530	45.2 ± 14.4	42.5 ± 14.4	−2.7 ± 13.6	<0.0001
Switchers[d] ($n=867$)							
Domain	Phase	Score range	n[b]	Baseline	EoT	CfB	*p*-value[c]
Pain	Premenstrual	35-125	865	44.6 ± 10.4	45.1 ± 11.4	0.5 ± 10.9	0.18
	Menstrual	31-120	864	44.5 ± 12.5	44.4 ± 13.5	−0.1 ± 13.4	0.78
Water retention	Premenstrual	32-120	864	42.3 ± 11.4	43.4 ± 13.1	1.1 ± 13.5	0.02
	Menstrual	32-126	864	42.8 ± 12.7	44.3 ± 14.7	1.5 ± 15.1	0.003
Impaired concentration	Premenstrual	40-157	864	44.7 ± 9.4	45.1 ± 9.8	0.4 ± 10.1	0.25
	Menstrual	39-159	863	43.9 ± 9.5	44.4 ± 10.6	0.5 ± 10.8	0.16
Negative Affect	Premenstrual	34-103	865	42.2 ± 10.5	42.7 ± 11.4	0.5 ± 11.0	0.21
	Menstrual	33-109	864	42.7 ± 11.8	42.6 ± 12.3	−0.1 ± 12.9	0.76

Data presented as mean ± standard deviation.
[a]Starters: participants who had not used hormonal contraception within 3 months prior to E4/DRSP initiation.
[b]Only includes participants who completed the MDQ at baseline and at end of treatment.
[c]Two-sided paired t-test with α set at 0.05.
[d]Switchers: participants who had used hormonal contraceptives within 3 months prior to E4/DRSP initiation.
CfB: change from baseline, DRSP: drospirenone; E4: estetrol; EoT: end of treatment; MDQ: menstruation distress questionnaire; N: number.

life [3,11–14]. Overall, mean baseline *t*-scores were in the normal range and, except for the scores for the domain 'Impaired Concentration', mean scores decreased at EoT. For hormonal contraception starters, the decreases in scores for the domains 'Negative Affect', 'Water Retention', and 'Pain' were significant whereas the switchers did not experience improvement. Starters had numerically higher baseline MDQ scores than switchers, potentially reflecting a pre-study beneficial effect on MDQ domains from prior hormonal contraceptive use. Switchers in our study reported minimal to no MDQ score changes, a finding different from starters, suggesting the beneficial effect from their prior hormonal contraceptive was maintained with E4/DRSP.

In the *t-score* analysis, starters reported improvements for premenstrual and menstrual symptoms across all four domains, with the largest changes noted for menstrual 'Pain' and the smallest for menstrual 'Impaired Concentration'.

Because we enrolled healthy women with low MDQ baseline scores, large changes in mean scores would not be expected. For that reason, we also performed shift analyses to describe changes from baseline for each symptom, providing more details on E4/DRSP impact for a specific sign or symptoms. The shift analysis primarily noted intensity shifts for 'Cramps', 'Backache' and 'Fatigue' in the domain 'Pain', for 'Painful or Tender Breast' and 'Swelling (Breast/Abdomen) in the domain 'Water Retention', and for 'Mood Swings' and 'Irritability' in the domain 'Negative Affect'. Consistent with the outcome of the *t-score* analysis, limited shifts were observed for symptoms in the domain of 'Impaired Concentration'.

Switchers reported minimal changes overall, although we did find a limited but statistically significant worsening of premenstrual and menstrual Water Retention. The changes in *t*-scores were small in comparison to those associated with the observed improvements in the trial. Such a limited worsening of premenstrual and menstrual water retention symptoms has also been described with MDQ evaluations in EE/DRSP users [13].

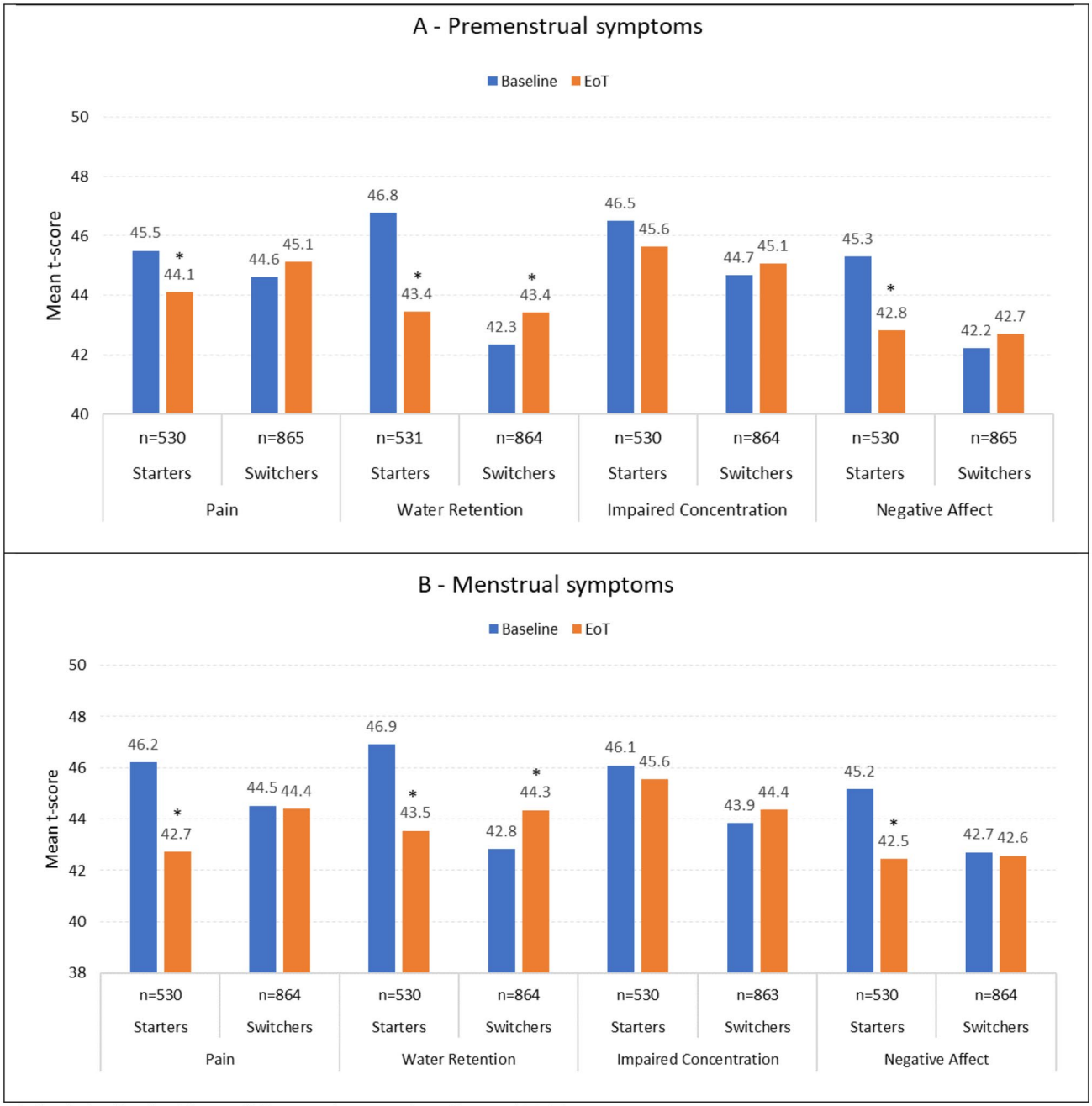
We did not observe clear changes in the domain Impaired Concentration. These findings align with the results of factor structure analyses conducted by Boyle [15], which indicated that Impaired Concentration is not an independent domain of the MDQ in a sample of young healthy women (mean age 21.1 years), 35% of whom were using an oral contraceptive. Boyle [15] suggested that Impaired Concentration might have emerged as a distinct factor of the MDQ if the analysis had been based on data from users with more severe symptoms.

Results in the context of what is known

Because hormonal contraceptive use can impact menstrual symptoms both positively and negatively [16–18], assessing the effect of a new COC is relevant. Negative effects on well-being and mental health have been linked to the oestrogen to progestogen ratio of contraceptives, age, and predisposing factors such as ongoing mental disorders, psychiatric symptoms, dysmenorrhoea, and premenstrual mood symptoms prior to OC use [19–22]. In addition, menstrual pain symptoms are common among women of reproductive age [23–25] and water retention that causes premenstrual breast tenderness can negatively impact women's quality of life as well [26–28].

COCs containing ethinylestradiol (EE) and levonorgestrel (LNG) are commonly prescribed. In 2016, Zethraeus and associates [29] reported the results of a double-blind randomised trial in 340 women who received EE 30 µg/LNG 150 µg or placebo for 3 months. Assessments using the Psychological General Well-Being Index and the Beck Depression Inventory showed that EE/LNG use decreased general well-being compared with placebo.

While EE/DRSP is considered frequently as a treatment for premenstrual syndrome (PMS), the data is generally of low-quality [30]. PMS may improve in the first three cycles of use but proven benefit thereafter as well as benefit in patients with less severe symptoms is limited [30]. However,



* Statistically significant difference between baseline and EoT.

DRSP: drospirenone; E4: estetrol; EoT: end of treatment; MDQ: menstrual distress questionnaire

Figure 1. Mean baseline and EoT premenstrual [A] and menstrual [B] MDQ *t*-scores for starters and switchers in the Europe/Russia phase 3 trial with E4/DRSP.

EE/DRSP is a proven treatment for premenstrual dysphoric disorder [30–34]. Overall, EE/DRSP appears more favourable in terms of mood symptoms than combination formulations with other progestins such as LNG [35,36]. A randomised, single-blind, seven cycle study using 21/7-day regimens of EE 30 µg/DRSP 3 mg and EE 30 µg/LNG 150 µg found that MDQ *t*-scores for the domains Water Retention and Impaired Concentration did not change and were comparable between both COCs [37]. EE/DRSP, however, was significantly better in alleviating negative affect symptoms during the menstrual phase (median *t*-score decrease −3; $p < 0.05$). In addition, more subjects in the EE/DRSP group reported significant improvement in physical well-being (60% vs 46%; $p < 0.05$).

Studies with E2/NOMAC suggest this COC has beneficial effects on menstrual symptoms and well-being/quality of life [11,38]. A pooled analysis from two clinical trials [11] showed that women who used E2/NOMAC (24/4 regimen, $n = 2631$) for 13 cycles reported decreases in MDQ *t*-scores for the domains Pain, Water Retention, Negative affect, Impaired Concentration, and Behaviour Change while changes with the comparator EE/DRSP (21/7 regimen, $n = 891$) were less pronounced. As in our study, starters had higher (i.e., worse) baseline scores than switchers, resulting in numerically greater decreases in *t*-scores for starters than for switchers (no inferential statistics calculated). Similar, but smaller benefits were observed for E2/NOMAC in the premenstrual phase. The premenstrual MDQ *t*-scores reported by women using E2/NOMAC were significantly different versus baseline in comparison to those reported by women using EE/DRSP (21/7 regimen), which could be related to a more hormone stable regimen with E2/NOMAC.

Table 4. Overview of shift analysis with % of participants remaining stable, improving and worsening and % of participants with severe or strong symptoms at baseline for premenstrual and menstrual symptoms in the Europe/Russia phase 3 trial with E4/DRSP - starters and switchers.

			Starters ($n=531$)				Switchers ($n=867$)			
			Severe/ strong symptoms at baseline	Change from baseline			Severe/ strong symptoms at baseline	Change from baseline		
Domain	Symptom	Stage		Stable	Improving	Worsening		Stable	Improving	Worsening
Pain	Muscle stiffness	Premenstrual	2.3%	81.3%	10.8%	8.0%	0.5%	81.8%	6.6%	11.6%
		Menstrual	3.6%	76.7%	14.2%	9.1%	0.9%	79.6%	7.9%	12.5%
	Headache	Premenstrual	3.0%	63.3%	19.3%	17.4%	5.1%	60.4%	21.0%	18.6%
		Menstrual	4.2%	62.4%	19.8%	17.8%	7.0%	***57.5%***	26.1%	16.4%
	Cramps	Premenstrual	4.5%	63.6%	21.9%	14.5%	2.9%	63.8%	17.8%	18.4%
		Menstrual	**16.4%**	**50.4%**	35.7%	14.0%	**11.0%**	**53.7%**	24.4%	21.9%
	Backache	Premenstrual	5.1%	66.0%	21.6%	12.5%	3.5%	64.0%	17.1%	18.8%
		Menstrual	**10.4%**	**59.5%**	28.5%	11.9%	7.1%	***58.5%***	21.3%	20.2%
	Fatigue	Premenstrual	7.2%	60.6%	21.8%	17.6%	5.0%	***53.2%***	21.2%	25.6%
		Menstrual	**10.2%**	**57.8%**	25.2%	17.0%	7.5%	***48.3%***	25.2%	26.5%
	General aches and pain	Premenstrual	2.3%	73.9%	14.2%	11.9%	1.4%	75.4%	13.0%	11.6%
		Menstrual	5.5%	66.9%	21.6%	11.6%	2.7%	68.0%	16.7%	15.3%
Water retention	Weight gain	Premenstrual	3.6%	67.2%	17.0%	15.8%	1.4%	72.2%	11.1%	16.7%
		Menstrual	3.0%	68.3%	18.2%	13.5%	1.7%	71.6%	10.3%	18.1%
	Skin blemish or disorder	Premenstrual	4.7%	68.7%	20.5%	10.7%	4.1%	60.1%	15.7%	24.2%
		Menstrual	5.5%	70.9%	18.9%	10.2%	3.6%	60.4%	16.1%	23.5%
	Painful or tender breasts	Premenstrual	**11.5%**	**49.4%**	34.5%	16.0%	5.2%	***58.3%***	23.3%	18.4%
		Menstrual	9.6%	***51.2%***	33.3%	15.5%	4.2%	***59.3%***	20.7%	19.9%
	Swelling	Premenstrual	8.5%	***53.5%***	29.7%	16.8%	3.2%	63.8%	18.5%	17.7%
		Menstrual	**10.0%**	**55.4%**	28.7%	15.9%	5.1%	60.4%	19.7%	19.9%
Negative Affect	Loneliness	Premenstrual	4.2%	74.9%	15.8%	9.2%	0.9%	79.3%	9.6%	11.1%
		Menstrual	4.4%	75.4%	15.0%	9.7%	1.5%	80.0%	9.6%	10.4%
	Anxiety	Premenstrual	3.0%	72.3%	16.8%	10.9%	1.3%	80.0%	8.6%	10.6%
		Menstrual	2.8%	73.5%	16.4%	10.0%	1.0%	78.8%	9.3%	11.9%
	Mood swings	Premenstrual	**13.8%**	**49.5%**	33.5%	17.0%	7.1%	***53.4%***	22.8%	23.8%
		Menstrual	**12.8%**	**47.9%**	34.9%	17.2%	6.8%	***49.1%***	26.5%	24.2%
	Crying	Premenstrual	4.9%	68.7%	20.0%	11.3%	2.9%	73.7%	14.0%	12.3%
		Menstrual	4.3%	69.6%	19.5%	11.0%	2.8%	72.2%	14.7%	13.1%
	Irritability	Premenstrual	**11.5%**	**53.1%**	31.0%	15.9%	6.5%	***52.0%***	23.4%	24.7%
		Menstrual	**13.2%**	**49.1%**	35.5%	15.5%	7.4%	***47.5%***	27.5%	25.0%
	Tension	Premenstrual	4.9%	66.0%	19.6%	14.3%	2.4%	67.2%	14.2%	18.5%
		Menstrual	4.9%	67.7%	19.8%	12.5%	2.9%	68.1%	15.9%	16.0%
	Feeling sad or blue	Premenstrual	4.3%	70.5%	19.1%	10.4%	2.1%	67.5%	16.3%	16.2%
		Menstrual	4.7%	69.2%	19.3%	11.5%	2.7%	64.2%	19.0%	16.8%
	Restlessness	Premenstrual	2.1%	81.3%	9.2%	9.4%	0.3%	80.8%	9.7%	9.5%
		Menstrual	2.1%	78.8%	10.6%	10.6%	1.7%	78.8%	11.1%	10.1%
Impaired concentration	Insomnia	Premenstrual	3.2%	78.6%	12.9%	8.5%	1.7%	81.4%	8.4%	10.2%
		Menstrual	4.5%	80.0%	11.9%	8.1%	2.1%	79.7%	10.4%	9.8%
	Forgetfulness	Premenstrual	1.9%	80.5%	9.9%	9.7%	1.3%	80.7%	9.0%	10.3%
		Menstrual	2.8%	76.9%	12.3%	10.8%	1.3%	79.8%	9.2%	11.0%
	Confusion	Premenstrual	0.0%	91.5%	4.5%	4.0%	0.7%	91.8%	3.8%	4.4%
		Menstrual	0.0%	89.4%	5.7%	4.9%	0.5%	90.8%	4.1%	5.1%
	Poor Judgement	Premenstrual	0.8%	90.7%	4.9%	4.3%	0.5%	91.7%	4.4%	3.9%
		Menstrual	0.8%	90.4%	4.5%	5.1%	0.2%	92.2%	3.8%	3.9%
	Difficulty concentrating	Premenstrual	1.7%	77.9%	12.3%	9.8%	1.2%	78.4%	9.6%	12.0%
		Menstrual	1.3%	73.2%	13.6%	13.2%	1.2%	78.7%	9.4%	11.9%
	Distractibility	Premenstrual	1.1%	76.0%	14.5%	9.4%	1.2%	77.1%	10.8%	12.2%
		Menstrual	1.7%	73.2%	15.5%	11.3%	1.2%	78.8%	10.3%	10.9%
	Minor accidents	Premenstrual	0.8%	89.4%	7.4%	3.2%	0.1%	91.7%	4.5%	3.8%
		Menstrual	0.4%	87.9%	7.4%	4.7%	0.3%	91.5%	4.3%	4.2%
	Poor motor coordination	Premenstrual	0.8%	91.7%	4.2%	4.2%	0.1%	93.1%	3.4%	3.6%
		Menstrual	0.4%	89.0%	5.9%	5.1%	0.2%	92.5%	3.1%	4.4%

Bold ≤60% of participants stable and ≥10% of participants with severe or strong symptoms at baseline.
Bold italic ≤60% of participants stable and <10% of participants with severe or strong symptoms at baseline.
Underlined: ≥10% difference between improvement and worsening.
DRSP: drospirenone; E4: estetrol.

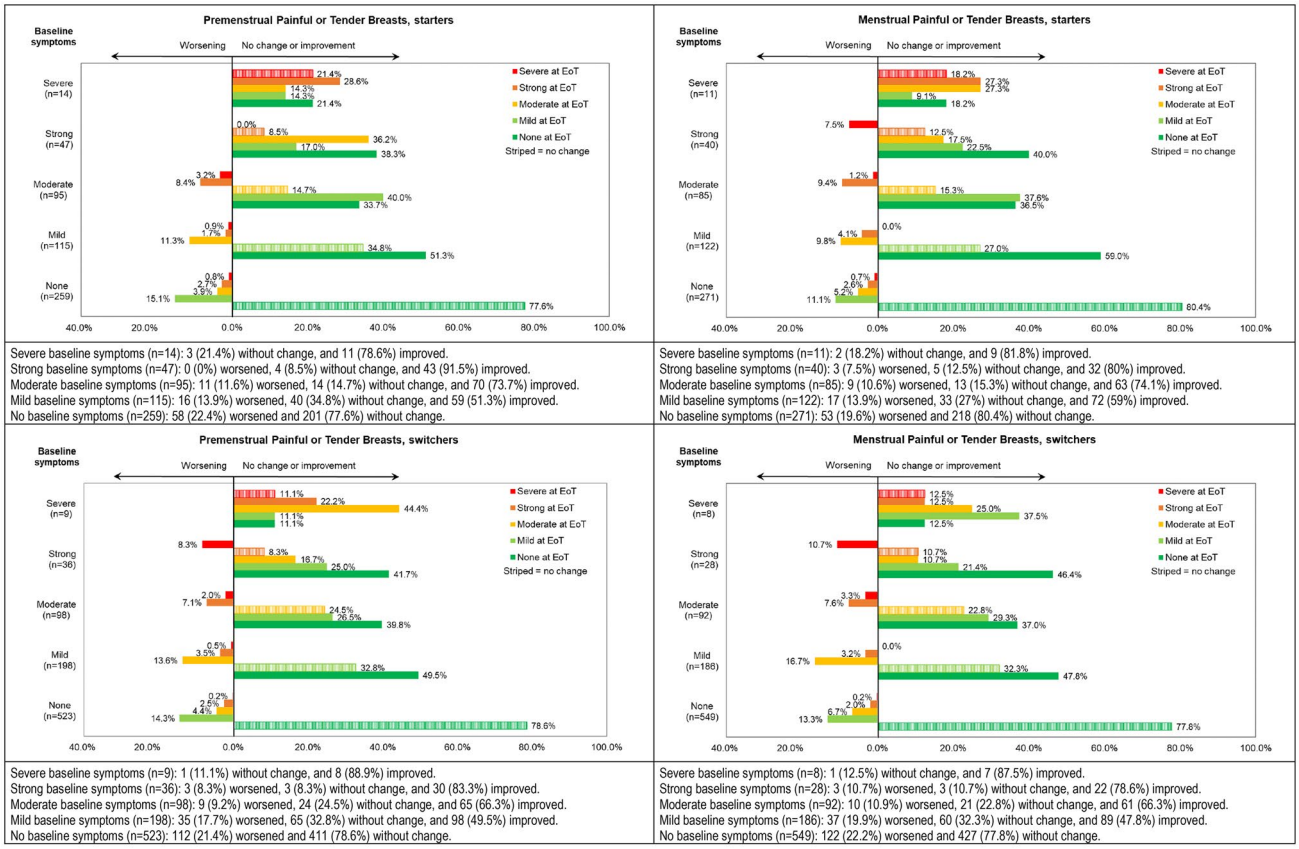
Clinical implications

In Phase 2 clinical trials, E4/DRSP caused negligible effects on endocrine, metabolic, and haemostasis parameters [39,40], and showed higher levels of user acceptability, well-being, and satisfaction than E4/LNG combinations [5].

Menstrual symptoms are a common reason for women to discontinue COC use which can increase the risk of unplanned pregnancies if other less reliable or no methods are used [20,41,42]. The positive effects on premenstrual and menstrual symptoms especially for starters as reported here are therefore important and make E4/DRSP a welcome addition to the contraceptive options available to women. Careful structured counselling when starting hormonal forms of birth control should be encouraged, taking into account the wishes of the user, efficacy, safety (e.g., VTE risk), and quality of life impact [43,44].

Research implications

Our analysis of the MDQ data shows a beneficial effect of E4/DRSP on physical and emotional premenstrual and menstrual symptoms, especially in hormonal contraceptive starters. Comparative clinical trials are required to evaluate these effects in relation to other COCs. Additionally, since we assessed the effects of E4/DRSP in a population with few participants having severe or strong symptoms at



Severe baseline symptoms (n=14): 3 (21.4%) without change, and 11 (78.6%) improved.
Strong baseline symptoms (n=47): 0 (0%) worsened, 4 (8.5%) without change, and 43 (91.5%) improved.
Moderate baseline symptoms (n=95): 11 (11.6%) worsened, 14 (14.7%) without change, and 70 (73.7%) improved.
Mild baseline symptoms (n=115): 16 (13.9%) worsened, 40 (34.8%) without change, and 59 (51.3%) improved.
No baseline symptoms (n=259): 58 (22.4%) worsened and 201 (77.6%) without change.

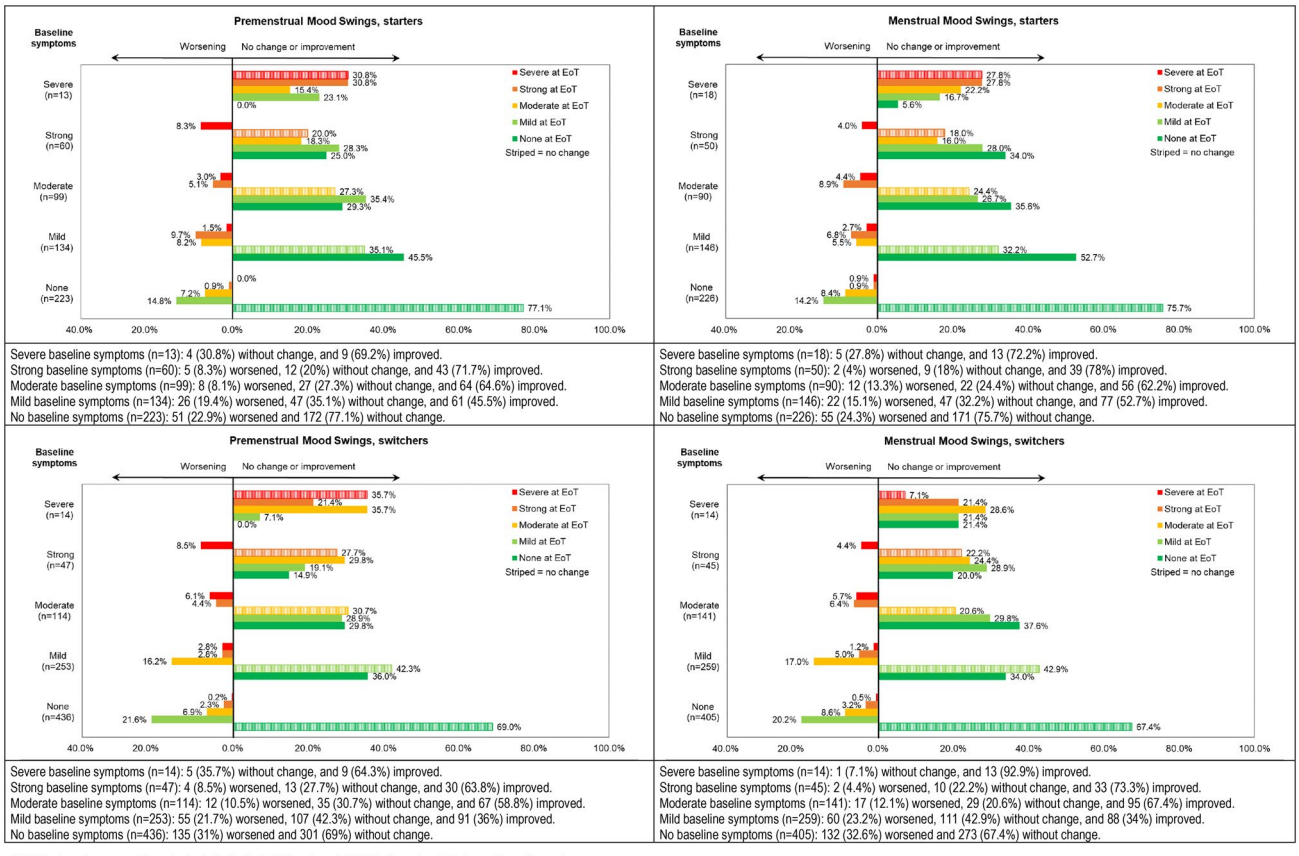
Severe baseline symptoms (n=11): 2 (18.2%) without change, and 9 (81.8%) improved.
Strong baseline symptoms (n=40): 3 (7.5%) worsened, 5 (12.5%) without change, and 32 (80%) improved.
Moderate baseline symptoms (n=85): 9 (10.6%) worsened, 13 (15.3%) without change, and 63 (74.1%) improved.
Mild baseline symptoms (n=122): 17 (13.9%) worsened, 33 (27%) without change, and 72 (59%) improved.
No baseline symptoms (n=271): 53 (19.6%) worsened and 218 (80.4%) without change.

Severe baseline symptoms (n=9): 1 (11.1%) without change, and 8 (88.9%) improved.
Strong baseline symptoms (n=36): 3 (8.3%) worsened, 3 (8.3%) without change, and 30 (83.3%) improved.
Moderate baseline symptoms (n=98): 9 (9.2%) worsened, 24 (24.5%) without change, and 65 (66.3%) improved.
Mild baseline symptoms (n=198): 35 (17.7%) worsened, 65 (32.8%) without change, and 98 (49.5%) improved.
No baseline symptoms (n=523): 112 (21.4%) worsened and 411 (78.6%) without change.

Severe baseline symptoms (n=8): 1 (12.5%) without change, and 7 (87.5%) improved.
Strong baseline symptoms (n=28): 3 (10.7%) worsened, 3 (10.7%) without change, and 22 (78.6%) improved.
Moderate baseline symptoms (n=92): 10 (10.9%) worsened, 21 (22.8%) without change, and 61 (66.3%) improved.
Mild baseline symptoms (n=186): 37 (19.9%) worsened, 60 (32.3%) without change, and 89 (47.8%) improved.
No baseline symptoms (n=549): 122 (22.2%) worsened and 427 (77.8%) without change.

DRSP: drospirenone, E4: estretrol, EoT: End of Treatment, MDQ: Menstrual Distress Questionnaire

Figure 2. Shift analysis for premenstrual and menstrual symptom scores for Painful or tender Breasts in the physical domain 'Water Retention' for starters and switchers who completed the MDQ at baseline and at end of treatment in the Europe/Russia phase 3 trial with E4/DRSP.



Severe baseline symptoms (n=13): 4 (30.8%) without change, and 9 (69.2%) improved.
Strong baseline symptoms (n=60): 5 (8.3%) worsened, 12 (20%) without change, and 43 (71.7%) improved.
Moderate baseline symptoms (n=99): 8 (8.1%) worsened, 27 (27.3%) without change, and 64 (64.6%) improved.
Mild baseline symptoms (n=134): 26 (19.4%) worsened, 47 (35.1%) without change, and 61 (45.5%) improved.
No baseline symptoms (n=223): 51 (22.9%) worsened and 172 (77.1%) without change.

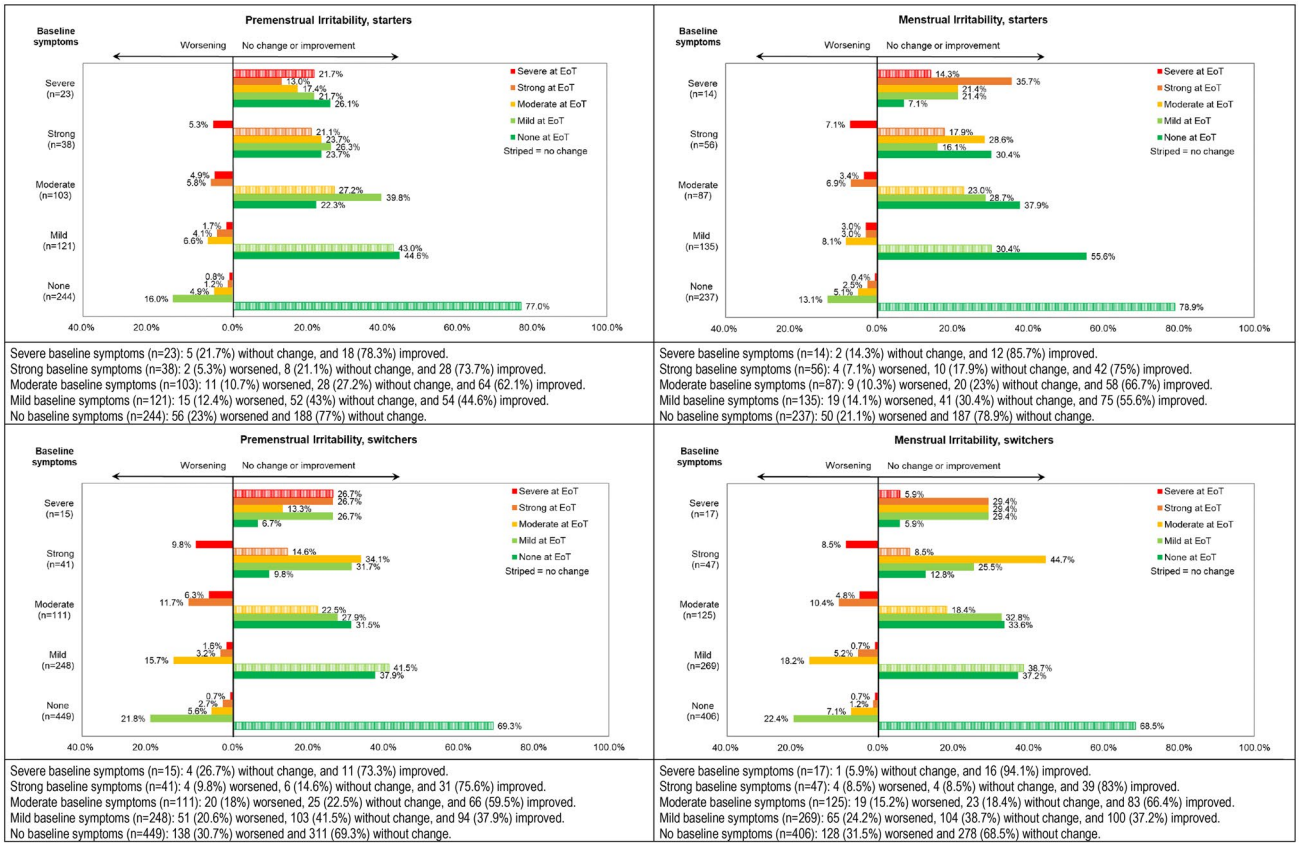
Severe baseline symptoms (n=18): 5 (27.8%) without change, and 13 (72.2%) improved.
Strong baseline symptoms (n=50): 2 (4%) worsened, 9 (18%) without change, and 39 (78%) improved.
Moderate baseline symptoms (n=90): 12 (13.3%) worsened, 22 (24.4%) without change, and 56 (62.2%) improved.
Mild baseline symptoms (n=146): 22 (15.1%) worsened, 47 (32.2%) without change, and 77 (52.7%) improved.
No baseline symptoms (n=226): 55 (24.3%) worsened and 171 (75.7%) without change.

Severe baseline symptoms (n=14): 5 (35.7%) without change, and 9 (64.3%) improved.
Strong baseline symptoms (n=47): 4 (8.5%) worsened, 13 (27.7%) without change, and 30 (63.8%) improved.
Moderate baseline symptoms (n=114): 12 (10.5%) worsened, 35 (30.7%) without change, and 67 (58.8%) improved.
Mild baseline symptoms (n=253): 55 (21.7%) worsened, 107 (42.3%) without change, and 91 (36%) improved.
No baseline symptoms (n=436): 135 (31%) worsened and 301 (69%) without change.

Severe baseline symptoms (n=14): 1 (7.1%) without change, and 13 (92.9%) improved.
Strong baseline symptoms (n=45): 2 (4.4%) worsened, 10 (22.2%) without change, and 33 (73.3%) improved.
Moderate baseline symptoms (n=141): 17 (12.1%) worsened, 29 (20.6%) without change, and 95 (67.4%) improved.
Mild baseline symptoms (n=259): 60 (23.2%) worsened, 111 (42.9%) without change, and 88 (34%) improved.
No baseline symptoms (n=405): 132 (32.6%) worsened and 273 (67.4%) without change.

DRSP: drospirenone, E4: estretrol, EoT: End of Treatment, MDQ: Menstrual Distress Questionnaire

Figure 3. Shift analysis for premenstrual and menstrual symptom scores for Mood Swings in the emotional domain 'Negative Affect' for starters and switchers who completed the MDQ at baseline and at end of treatment in the Europe/Russia phase 3 trial with E4/DRSP.



DRSP: drospirenone, E4: estretrol, EoT: End of Treatment, MDQ: Menstrual Distress Questionnaire

Figure 4. Shift analysis for premenstrual and menstrual symptom scores for Irritability in the emotional domain 'Negative Affect' for starters and switchers who completed the MDQ at baseline and at end of treatment in the Europe/Russia phase 3 trial with E4/DRSP.

baseline, studies evaluating E4/DRSP in patients specifically with significant symptoms are needed to understand the impact in those populations.

Strengths and limitations

We performed our analysis in a large sample of users without pre-existing major menstrual complaints thus allowing to assess negative and positive changes which have proven to be important for adherence and satisfaction. We used the validated Moos MDQ questionnaire, which is generally used to track improvement in menstrual symptoms when on contraception and was also used in studies with other COCs. In addition to the standard MDQ *t-scores* analysis, we also analysed the shifts in individual symptoms within each domain. This approach enabled us to identify the symptoms that are responsible for the changes within the domains. Source data verification was performed as part of study quality control. The main goal of our Phase 3 trial was to assess the contraceptive efficacy and safety of E4/DRSP and the MDQ *t*-score analysis was a planned secondary objective, while the presentation of the shift analysis was performed post hoc. Consequently, the trial was not specifically designed for MDQ analysis, and no criteria were used to enrol participants with menstrual-related complaints. The trial did not include comparators and predisposing factors were not assessed. Also, information on the specific content of oral contraceptives used before entering the trial was not obtained. A more regular assessment (e.g., at baseline, 3, 6, 9 and 12 months) in women with higher MDQ baseline scores could have added more insight in the timing of the response to E4/DRSP on the burden of menstruation symptoms.

The study did not include the assessment of the individual patient's rating of the observed changes in the symptoms and, therefore, cannot directly relate statistical to clinical significance, but it provides indirect evidence on patients' positive or negative experiences related to menstrual symptoms. Shift analyses revealed more informative insights into specific symptom changes, highlighting significant improvements particularly in individuals with more severe symptoms at baseline.

Conclusions

The analysis of MDQ responses of 1,398 E4/DRSP phase 3 trial participants in Europe and Russia showed that starters experienced improvements in the domains Pain, Negative Affect, and Water Retention. Switchers showed minimal changes in the domain Water Retention.

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Ethical approval

The study design was based on the Declaration of Helsinki, ICH E6 (R2) Good Clinical Practice guidelines, US Food and Drug Administration and European Medicines Agency (EMA) guidelines. The trial centre Independent Ethics Committees approved the trial at the different study sites. The full list of Ethics committees and approval dates was previously published Gemzell-Danielsson et al. (2022) [6].

Disclosure statement

JB Invited lecturer and advisor receiving honoraria from Bayer AG, MSD, Exeltis, Gedeon Richter, Actavis, Theramex, Labatec, Abbott, Mithra, Libbs.

CB serves on the Advisory Boards of Bayer AG, Bayer Canada, Astellas, BioSyent and has received honoraria from Merck Canada, Pfizer, Lupin Pharma, Astellas and research grants from Incyte, Mylan and Exeltis.

JZ has no conflict of interest to declare.

SW serves on an advisory board for Bayer and MSD.

TP serves on an Advisory Board for Exeltis, Merck and has received honoraria from Astra Zeneca, Exeltis, Ferring, Merck and MSD. Her research is funded by the Finnish Academy, Sigrid Jusélius Foundation, the Finnish Medical Foundation and Roche.

LS serves as a consultant for Bayer Pharmaceuticals (Russia) and for Gedeon Richter (Russia)

IA has served as an ad hoc speaker for Bayer Pharma AG (Russia), TEVA (Russia), Astellas (Russia), Roche Diagnostics Rus LLC (Russia), Avexima, Bionorica (Russia), CSC Pharma, and Aspen Health LLC.

KGD has served as an ad hoc speaker and/or member of advisory boards for Exelgyn, Campus Pharma,HRA Pharma, Exeltis, Bayer AG, Organon (MSD), MedinCell, Gedeon Richter, Natural Cycles, Cirqle and Myovant.

MJ is employee of Mithra Estetra SRL, an affiliate company of Mithra Pharmaceuticals, Liège, Belgium.

MDC has received speaking honorarium from Gedeon Richter, Mayne, OLIC, and Organon, served on an Advisory Board for Gedeon Richter and Mayne, has stock options with Femasys, and has consulted for Curai, Estetra SRL, Medicines360, and Organon. The Department of Obstetrics and Gynaecology, University of California, Davis, receives contraceptive research funding for MDC from Chemo Research SL, Evofem, Femasys, Medicines360, Merck, Sebela, and Sumitomo Pharma.

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