

Treatment preferences among Japanese women with dysmenorrhea: results from a discrete choice experiment study

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Purpose: To examine patient preferences for oral and intrauterine system treatments for dysmenorrhea in Japan.

Patients and methods: A discrete choice experiment was conducted to assess the willingness to accept trade-offs among hypothetical treatment profiles. An internet-based survey was administered to women 18–49 years of age who self-reported a dysmenorrhea diagnosis or experienced dysmenorrhea at least once in the past 6 months (N=309). Choice questions included pairs of treatments presented with different attributes: mode of administration, reduction in bleeding after 6 months, chance of symptoms becoming “improved”, nausea, weight gain, irregular bleeding, and risk of venous thromboembolism. Relative importance (RI) estimates were computed.

Results: The mean respondent age was 35.8 years (standard deviation =7.0), and 85 women (27.5%) reported that they had previously used hormonal therapy for dysmenorrhea. Treatment preference was most strongly associated with mode of administration (RI=49.8%), followed by chance of irregular bleeding (RI=17.3%). In contrast, treatment preference was most weakly associated with chance of weight gain (RI=2.4%) and reduction in bleeding after 6 months (RI=0.8%). Respondents preferred oral treatments: for twice-daily regimen, odds ratio (OR)=4.90; for once-daily fixed cyclic regimen, OR=4.20; and for once-daily flexible extended regimen, OR=2.44; whereas for intrauterine system, OR=0.02 ($p<0.001$ for all). Those with prior hormonal therapy experience exhibited the same pattern.

Conclusion: Mode of administration factored heavily in dysmenorrhea treatment preferences. Women of reproductive age preferred oral medication, especially twice-daily regimen and once-daily fixed cyclic regimen. Findings can potentially help to improve physician–patient communication and treatment decision making. Physicians should consider factors that can influence patient preference to optimize treatment acceptance and adherence.

Keywords: menstrual cramps, hormonal therapy, intrauterine system, oral regimen, patient preference, treatment administration, treatment attributes

Introduction

Dysmenorrhea is defined as a severe, painful, cramping sensation in the lower abdomen that is often accompanied by other symptoms, such as sweating, headaches, nausea, vomiting, diarrhea, and tremulousness, all occurring just before or during the menses.¹ There are two types of dysmenorrhea: primary and secondary.^{1,2} Primary dysmenorrhea refers to pain with no obvious pathological pelvic disease and almost always first occurs in women 20 years of age or younger, once their ovulatory cycles become established.¹ Secondary dysmenorrhea is caused by underlying pelvic conditions or

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other pathological conditions and is more common in women older than 20 years old.^{1,2}

The prevalence of dysmenorrhea can vary considerably, depending on the method of assessment.³ In one of the few epidemiological studies conducted in Japan, Ohde et al found that approximately 15.8% of women aged 18–51 reported experiencing dysmenorrhea.⁴ Another more recent observational study of Japanese women aged 15–49 found that, among those who had visited a gynecologist in the past 3 months for menstrual symptoms, 19.7% self-reported a diagnosis of dysmenorrhea.⁵ Yet, data from two large-scale cross-sectional survey studies in Japan suggest the prevalence of dysmenorrhea may actually be higher, as menstrual pain was reported by 50.4%–77.6% of women.^{6,7}

For women who experience dysmenorrhea, there is a significant effect on their health-related quality of life and daily activities.^{8–11} A prospective observational study of emergency room patients indicated that women who presented with dysmenorrhea and individuals who presented with renal colic reported a comparable level of pain intensity.¹² Additionally, decrements in health utilities for dysmenorrhea were similar to those associated with chronic migraine.¹³ Thus, the humanistic burden and debilitating effects attributed to dysmenorrhea are substantial.

Dysmenorrhea also poses a considerable economic burden, given its impact on work productivity and health care resource utilization.^{14,15} Dysmenorrhea is responsible for considerable direct and indirect economic losses due to the costs of medications, medical care, and decreased productivity.¹ Taketani conducted a large survey-based study of 4,230 Japanese women to evaluate the burden of dysmenorrhea and reported that one-third of the women required medical intervention because of their symptoms.¹⁶ A retrospective analysis of Japanese claims data showed that, in the year after diagnosis, women with dysmenorrhea incurred two to three times the direct costs incurred by matched controls.¹⁵ Furthermore, Tanaka et al reported that the total economic burden to Japanese society associated with menstrual symptoms was approximately ¥682.8 billion (\$8.6 billion US dollars), with work productivity loss accounting for 72% of the total cost.⁶

There are several treatment options available for dysmenorrhea. NSAIDs have been recommended as a first-line treatment option, although oral, intravaginal, and intrauterine hormonal contraceptives also represent appropriate options, particularly for women who desire contraception along with treatment for their dysmenorrhea.^{17–19} NSAIDs, LEPs, and IUS are primarily recommended in Japan; traditional Chinese

medicine and anti-cramp medicine can also be used to treat primary dysmenorrhea.²⁰ These treatment options can vary significantly with respect to their mode of administration, dosing characteristics, effectiveness, and safety. In Japan, two kinds of COCs are available on the market: LEPs, which are reimbursed for dysmenorrhea treatment, and other COCs for contraceptive purposes, which are not reimbursed.

A systematic review reported that NSAIDs are highly effective for relieving dysmenorrhea pain, with similar efficacy demonstrated across formulations. However, NSAIDs are ineffective for, or are not tolerated by, approximately 15% of women with dysmenorrhea.¹⁴ In a longitudinal cohort study, the use of levonorgestrel-releasing IUSs or COCs was related to a significant decrease over time in dysmenorrhea severity, compared with other methods of contraception (eg, copper intrauterine device, condoms, or barrier methods) or no contraception use.²¹ However, COCs may be contraindicated for women who are at risk for VTE, and levonorgestrel-releasing IUS has been associated with various side effects, such as menstrual irregularity, amenorrhea, ovarian cysts, acne, increases in weight, depressed mood, and a reduction in libido.^{22,23}

Despite the sizeable burden attributed to dysmenorrhea and the effectiveness of treatment, this condition is underdiagnosed and undertreated.²⁴ Because it is so common, women may erroneously view menstrual pain as being normal and thus may not bring their symptoms to the attention of a health care provider. This idea is supported by a recent prospective, cross-sectional survey of female Jordanian college students in which over three-quarters self-reported experiencing menstrual pain, yet <10% of these respondents sought medical treatment.²⁵ This is also likely the case in Japan, as cross-sectional population studies have shown that only 12%–20% of women who reported experiencing menstrual pain consulted with a health care provider about treatment.^{6,16} Additionally, religious or cultural beliefs, as well as negative societal attitudes toward menstruation, may not only inhibit women from broaching the topic with their health care provider but also make it less likely that clinicians will raise this issue with their patients.²⁴ As such, a better understanding of the factors underlying treatment decisions will be integral to informing strategies to improve treatment rates.

Objective

Prior research has suggested that adherence can be maximized when treatment is aligned with patient preferences.²⁶ Therefore, the aim of this study was to understand how women with dysmenorrhea value different aspects of

treatments for dysmenorrhea, which can potentially help to improve treatment decision making. Specifically, this study aimed to quantify the trade-offs patients with dysmenorrhea in Japan are willing to make between different product attributes, including mode of administration (oral vs IUS), effectiveness and other patient benefits (chance of symptoms becoming “improved” and chance of reduction in bleeding after 6 months), and treatment tolerability and safety (chance of nausea, chance of weight gain, chance of irregular bleeding, and risk of VTE), by eliciting patient preferences associated with treatments like levonorgestrel-releasing IUS, drospirenone/ethinyl estradiol tablets with a flexible extended regimen, norethisterone/ethinyl estradiol tablets, and dienogest. This study sought to represent potential real-world patient choices as accurately as possible, although limited to the Japanese population.

Methods

Pilot testing

Prior to this patient preference research, a qualitative stage incorporating cognitive interviews (N=10 women with dysmenorrhea) was conducted, which assessed the validity of the survey instrument to be used in the main quantitative study by investigating the appropriateness, clarity, and completeness of the instructions, attributes, levels, and discrete choice questions. Inclusion and exclusion criteria for the interviews were the same as those described in the main study section. Written informed consent was obtained from all pilot test participants. The protocol of the pilot-stage qualitative interviews was reviewed and approved by the Pearl Institutional Review Board (Study Number 16-KANT-129) in Indianapolis, IN, USA. The attributes and levels used in the qualitative interviews were initially developed from clinical data found in literature reviews of clinical trials and other relevant research findings. The cognitive qualitative interviewing helped to further refine the list of attributes and levels to ensure the main study only included those most relevant to the patients when making treatment decisions, while also being easy to understand. After reviewing the results with study team members, the final survey instrument was created for the main observational quantitative study.

Main study

A DCE method was used. The DCE is a survey approach designed to assess respondents’ willingness to accept trade-offs among hypothetical treatment profiles described by treatment attributes of varying levels. The DCE method is rooted in economic theory and is based on the principle that

products can be described by various attributes. In a health care context, the attractiveness of a treatment to patients depends on patients’ relative preferences for treatment attributes expressed by their willingness to accept trade-offs among them. Although there are alternatives to eliciting patient preferences (eg, revealed preferences, direct ratings/rankings, etc), DCE is one of the most common approaches for assessing preferences in a health care context.²⁷

To generate the necessary data for the analyses, this study was conducted with 309 women with dysmenorrhea using a web-based survey. These women were recruited from patients who had indicated in a prior survey that they had previously experienced dysmenorrhea. To be included in the study, female respondents had to be aged 18–49 years old, able to read and understand Japanese, and provide informed consent. Additionally, to be eligible to participate, respondents had to have self-reported being diagnosed with dysmenorrhea by a physician, experienced menstrual cramps (dysmenorrhea) in at least one menstrual cycle in the past 6 months, or had menstrual cramps in one of the past three menstrual cycles. Pregnant or postmenopausal women were ineligible for this study. Informed consent was obtained electronically prior to starting the web-based survey.

The survey included a series of preference elicitation questions, each asking respondents to choose between two hypothetical treatments for dysmenorrhea shown side by side (no real treatments or treatment names were used or mentioned in the survey). Predictive probabilities were then estimated to determine whether patients were more likely to choose one hypothetical treatment over another. Each hypothetical treatment alternative shown in the preference elicitation questions was defined by various attributes (eg, mode of administration, chance of symptoms becoming “improved”, or risk of VTE), which were developed from prior literature and input from a clinical expert and then refined after patient cognitive interviews. The experimental design (ie, the combination of attributes and levels that were presented to respondents) was developed using the D-optimal algorithm available in SAS version 9.3 using input from the qualitative cognitive interviews,²⁸ which helped to determine the wording and the final number of the attributes and levels to be tested in this quantitative study. This method ensured that there were a sufficient number of respondents and number of choice questions presented, that the importance of the contributions of the individual attributes could be isolated from the rest of the (possibly confounding) effects presented simultaneously, and that all attributes and levels were exposed an equal number of times in the DCE. Figure 1 represents an example of a single

preference elicitation question that was presented to respondents; they were also provided additional information defining irregular bleeding and VTE. After reviewing the information in the two presented profiles, the respondent was asked to

select which of the two profiles (Medicine A or B) she would prefer as her dysmenorrhea treatment. In total, respondents were shown nine comparisons to be used in the analyses, plus two additional cards for the purposes of quality control and

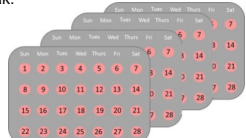
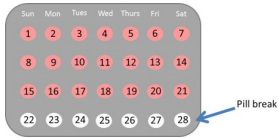










Medicine feature	Medication A	Medication B
Mode of administration Hormonal therapy with extended regimen (maximum 120 days): Oral daily pill is taken for 120 days and a 4-day pill break follows. This cycle is repeated. A pill should be continuously taken for first 24 days regardless of irregular bleeding during those 24 days. A 4-day pill break should be taken only if irregular bleeding (including spotting) occurs for 3 consecutive days after the first 24 days of taking the pill. Administration of the pill should be resumed after the 4-day pill break according to the baseline administration cycle of 120 days. Generally, unless you do not experience irregular bleeding, no menstrual bleeding occurs during administration of the drug, but bleeding starts during a pill break. 	Hormonal therapy with a fixed cyclic regimen: Oral daily pill for 21 days followed by 7 days of pill break. This cycle is repeated; no menstrual bleeding occurs during administration of the drug, but starts during a pill break. 	
Chance of symptoms becoming "improved"	80% of women experiencing "improved" symptoms 	65% of women experiencing "improved" symptoms 
Chance of nausea	12% of women experiencing nausea 	24% of women experiencing nausea 
Chance of weight gain	9% of women experiencing weight gain 	0% of women experiencing weight gain 
Reduction in the amount of bleeding after 6 months	85% of women experiencing less bleeding 	65% of women experiencing less bleeding 
Chance of irregular bleeding	35% of women experiencing irregular bleeding 	35% of women experiencing irregular bleeding 
Risk of VTE	About one case of VTE will occur among 10,000 women over an average of 1 year	About 10 cases of VTE will occur among 10,000 women over an average of 1 year
If these were the only medicines available, which would you choose?	<input type="checkbox"/> Medicine A	<input type="checkbox"/> Medicine B

Figure 1 Example preference elicitation task. Abbreviation: VTE, venous thromboembolism.

validity estimation. The main quantitative study protocol was approved by the Ethics Committee of the nonprofit organization, Clinical Research Promotion Network Japan.

Measures

Demographics

Demographic information was self-reported by patients and included age, education, marital status, region of residence, employment status, income, and health insurance.

Comorbidities

Respondents were asked to indicate whether they experienced any of the following comorbidities: headache, lower back pain, lower abdominal pain, migraine, hay fever, nasal allergies, dry eye, acne, chronic constipation, eczema, insomnia, heartburn, anemia, irregular bleeding, nausea, heavy menstrual bleeding, vaginitis, or primary ovarian dysfunction; or whether they were diagnosed with any of the following conditions by a health care provider: endometriosis, endometrial cancer, adenomyosis, uterine fibroids, pulmonary embolism, or retinal thrombosis.

Health history

Health history variables included self-reported height and weight (used to calculate BMI category), date of dysmenorrhea diagnosis (if applicable), number of menstrual cycles out of the last three that were accompanied by menstrual cramps (dysmenorrhea), number of weeks since last experienced dysmenorrhea, number of days experiencing dysmenorrhea per cycle, number of days experiencing menstrual bleeding per normal menstrual cycle, level of dysmenorrhea pain (using a visual analog scale), any experience of seeking gynecologist consultation, previous and current treatments for dysmenorrhea, and number of previous pregnancies and deliveries.

Work productivity

Respondents were also asked to self-report on the level of work productivity loss they experienced over the past 3 months and the past 6 months due to dysmenorrhea using a measure that was based on a prior study of dysmenorrhea in Japan.⁶ The specific items and response options were as follows: during the previous 3 (or 6) months, I was absent from work/school work/household chores due to dysmenorrhea symptoms (yes/no; if yes, respondent was asked to report the total number of days); during the previous 3 (or 6) months, I decreased work/school work/household chores volume or time due to dysmenorrhea symptoms (yes/no; if yes, respondent was asked to report the total number of days);

during the previous 3 (or 6) months, there were days I had decreased efficiency in work/school work/household chores due to dysmenorrhea symptoms (yes/no; if yes, respondent was asked to report the total number of days).

Attribute categories

There were seven attribute categories, each with multiple levels: mode of administration (four levels), reduction in the amount of bleeding after 6 months (three levels), chance of symptoms becoming “improved” (three levels), chance of nausea (three levels), chance of weight gain (three levels), chance of irregular bleeding (three levels), and risk of VTE (two levels). A description of attribute categories and levels is shown in Table 1.

Treatment choice

The primary end point was treatment choice. Specifically, respondents were asked to choose between hypothetical Medicine A and Medicine B.

Analysis

The analyses were performed using the software package SAS release 9.3 (SAS Institute Inc., Cary, NC, USA) and Sawtooth’s Software CBC HB release 4.4.0.

Demographics and baseline characteristics

The study sample was described with respect to demographics, comorbidities, health history, and work productivity using frequencies and percentages for categorical variables. Means, SDs, medians, and ranges, when appropriate, were reported for continuous variables.

Patient preferences

The choice data were analyzed using a hierarchical Bayesian logistic regression model. The outcome variable of this model was choice, and the predictor variables were the levels within each attribute (ie, mode of administration, reduction in the amount of bleeding after 6 months, chance of symptoms becoming “improved”, chance of nausea, chance of weight gain, chance of irregular bleeding, and risk of VTE). Effects coding parameterization was used for each level within each attribute. Overall goodness-of-fit was examined using the root likelihood, which indicates how much better the model is at predicting the data, compared with chance. The resulting parameter estimate for each attribute level represents the preference weight, which is defined as the marginal utility of a change in the levels tested within a given attribute. Except for mode of administration, interpolations

Table 1 Description of attribute categories and levels

Attribute	Levels
Mode of administration	Hormonal therapy with extended regimen (maximum 120 days); oral daily pill is taken for 120 days; 4-day pill break follows; this cycle is repeated; a pill should be continuously taken for first 24 days regardless of irregular bleeding during those 24 days; a 4-day pill break should be taken only if irregular bleeding (including spotting) occurs for 3 consecutive days after the first 24 days of taking the pill; administration of the pill should be resumed after the 4-day pill break according to the baseline administration cycle of 120 days; generally, unless you do not experience irregular bleeding, no menstrual bleeding occurs during administration of the drug, but bleeding starts during a pill break
	Intrauterine device, long-term hormonal therapy that lasts for 5 years; do not have to be taken daily; a T-shaped device is inserted from the vagina at an outpatient clinic (size of device: 3 cm); after insertion, a periodic check is needed after 3, 6, and 12 months by a doctor; an annual check is also needed when continuing over 1 year; when expecting pregnancy, it can be removed from the uterus; generally, no menstrual bleeding occurs during administration of the drug
	Hormonal therapy with a fixed cyclic regimen; oral daily pill is taken for 21 days followed by 7 days of pill break; this cycle is repeated; no menstrual bleeding occurs during administration of the drug, but starts during a pill break
Chance of symptoms becoming "improved"	Hormonal therapy; twice-daily pill; no menstrual bleeding occurs during administration of the drug
	50% of women experiencing "improved" symptoms
	65% of women experiencing "improved" symptoms
Chance of nausea	80% of women experiencing "improved" symptoms
	0% of women experiencing nausea
	12% of women experiencing nausea
Chance of weight gain	24% of women experiencing nausea
	0% of women experiencing weight gain
	4% of women experiencing weight gain
Reduction in the amount of bleeding after 6 months	9% of women experiencing weight gain
	65% of women experiencing less bleeding
	75% of women experiencing less bleeding
Chance of irregular bleeding	85% of women experiencing less bleeding
	1% of women experiencing irregular bleeding
	35% of women experiencing irregular bleeding
Risk of VTE	70% of women experiencing irregular bleeding
	About one case of VTE will occur among 10,000 women over an average of 1 year
	About 10 cases of VTE will occur among 10,000 women over an average of 1 year

Abbreviation: VTE, venous thromboembolism.

were made to determine the marginal utilities for the values contained within the numeric range tested for each attribute. Parameter estimates for the levels tested were reported along with their standard errors, 95% confidence intervals, and nominal *p*-values.

These parameter estimates were also used to calculate RIs using a sum-of-squares approach.²⁹ For each attribute, the regression coefficients for each level of that attribute were squared and summed together. The resulting sums of squares were divided by the attribute-specific degrees of freedom to generate an MSS for each attribute. The RI of each attribute was calculated by dividing the MSS for that attribute by the sum of all MSS values for all attributes. Attributes with higher RIs have a disproportionately larger MSS than other attributes, which is due to larger differences in the observed preference of the individual levels. Ninety-five percent confidence intervals were also reported. RI analyses, as described above, were repeated using data from the subset of respondents who

reported having previously used hormonal therapy to treat their dysmenorrhea (*n*=85) to examine whether results could be replicated among women with prior treatment experience.

Results

Demographics and baseline characteristics

Among the total of 309 women with dysmenorrhea who participated, patients had a mean age of 35.8 years (*SD*=7.0) (Table 2), including 71 women in the 18- to 29-year-old age bracket, 135 in the 30- to 39-year-old age bracket, and 103 in the 40- to 49-year-old age bracket. A plurality of respondents reported being employed full time (41.8%), having a 4-year college degree (41.8%), and being from the Kanto region (41.1%). Most respondents were single/divorced (61.2%) and reported a household income of <¥7,500,000 (63.4%). Similar proportions of respondents indicated having national health insurance (48.9%) and employees' health insurance (49.2%).

Table 2 Demographic characteristics of the full study sample (N=309)

Variable	Total (N=309)
Age, mean \pm SD	35.80 \pm 7.00
Age category	
18–29 years, n (%)	71 (22.98%)
30–39 years, n (%)	135 (43.69%)
40–49 years, n (%)	103 (33.33%)
Highest level of education	
Junior high school, n (%)	4 (1.29%)
High school, n (%)	74 (23.95%)
Vocational school, n (%)	44 (14.24%)
2-year university, n (%)	45 (14.56%)
4-year university, n (%)	129 (41.75%)
Graduate school, n (%)	13 (4.21%)
Marital status	
Married/living with partner, n (%)	120 (38.83%)
Single/divorced, n (%)	189 (61.17%)
Region	
Hokkaido, n (%)	15 (4.85%)
Tohoku, n (%)	26 (8.41%)
Kanto, n (%)	127 (41.10%)
Chubu, n (%)	45 (14.56%)
Kinki, n (%)	57 (18.45%)
Chugoku, n (%)	10 (3.24%)
Shikoku, n (%)	7 (2.27%)
Kyushu, n (%)	22 (7.12%)
Employment status	
Full time, n (%)	129 (41.75%)
Self-employed, n (%)	17 (5.50%)
Part time, n (%)	61 (19.74%)
Homemaker, n (%)	51 (16.50%)
Retired, n (%)	0 (0.00%)
Student, n (%)	6 (1.94%)
Long-term disability, n (%)	8 (2.59%)
Short-term disability, n (%)	1 (0.32%)
Not employed, but looking for work, n (%)	16 (5.18%)
Not employed and not looking for work, n (%)	22 (7.12%)
Household income	
<¥2,500,000, n (%)	44 (14.24%)
¥2,500,000–¥4,999,999, n (%)	86 (27.83%)
¥5,000,000–¥7,499,999, n (%)	66 (21.36%)
¥7,500,000–¥9,999,999, n (%)	39 (12.62%)
¥10,000,000–¥12,499,999, n (%)	11 (3.56%)
¥12,500,000–¥14,999,999, n (%)	9 (2.91%)
\geq ¥15,000,000, n (%)	4 (1.29%)
Unknown, n (%)	50 (16.18%)
Health insurance	
National health insurance, n (%)	151 (48.87%)
Employees' health insurance, n (%)	152 (49.19%)
None of the above; all treatment costs paid by patient, n (%)	6 (1.94%)

Abbreviation: SD, standard deviation.

As shown in Table 3, the most frequently reported dysmenorrhea-related comorbidities currently experienced, experienced in the past, or ever diagnosed were acne (72.8%), headache (71.5%), and lower back pain (59.6%). In contrast,

Table 3 Dysmenorrhea-related comorbidities for the full study sample (N=309)

Variable	Total (N=309)
Conditions that are currently being experienced or were experienced in the past	
Acne, n (%)	225 (72.82%)
Headache, n (%)	221 (71.52%)
Lower back pain, n (%)	184 (59.55%)
Nausea, n (%)	170 (55.02%)
Lower abdominal pain, n (%)	166 (53.72%)
Migraine, n (%)	154 (49.84%)
Anemia, n (%)	151 (48.87%)
Nasal allergies, n (%)	140 (45.31%)
Eczema, n (%)	126 (40.78%)
Hay fever, n (%)	124 (40.13%)
Heartburn, n (%)	119 (38.51%)
Dry eye, n (%)	117 (37.86%)
Irregular bleeding, n (%)	106 (34.30%)
Chronic constipation, n (%)	98 (31.72%)
Insomnia, n (%)	93 (30.10%)
Heavy menstrual bleeding, n (%)	56 (18.12%)
Vaginitis, n (%)	39 (12.62%)
Primary ovarian dysfunction, n (%)	1 (0.32%)
None of the above, n (%)	8 (2.59%)
Conditions that were diagnosed by a health care provider	
Endometriosis, n (%)	34 (11.00%)
Uterine fibroids, n (%)	31 (10.03%)
Adenomyosis, n (%)	8 (2.59%)
Endometrial cancer, n (%)	1 (0.32%)
Pulmonary embolism, n (%)	0 (0.00%)
Retinal thrombosis, n (%)	0 (0.00%)

those comorbidities reported least often by participants included primary ovarian dysfunction and endometrial cancer (for each, 0.3%), as well as pulmonary embolism and retinal thrombosis (for each, 0.0%).

Patients who had been diagnosed (n=103 [33.3%]) with dysmenorrhea were diagnosed, on average, 11.0 years prior (SD=8.0) (Table 4). Almost two-thirds (63.4%) were of normal weight. Approximately three-quarters of respondents (74.4%) had never been pregnant, but among those who had previously been pregnant, a plurality (39.2%) reported giving birth one time. Of the last three menstrual cycles, most respondents reported experiencing dysmenorrhea in all three cycles (71.2%). Dysmenorrhea was last experienced a median of 3.0 (range=1.0–26.0) weeks prior and was experienced a median of 2.0 (range=0.0–28.0) days per menstrual cycle. On a scale of 0 (no pain) to 10 (the worst imaginable pain), dysmenorrhea pain in the typical menstrual cycle and in the most recent menstrual cycle was rated a mean of 6.2 (SD=2.1) and 5.8 (SD=2.2), respectively. Approximately half of the sample was currently being

Table 4 Health history for the full study sample (N=309)

Variable	Total (N=309)
BMI, mean \pm SD	21.00 \pm 4.00
BMI, category	
Underweight, n (%)	75 (24.27%)
Normal weight, n (%)	196 (63.43%)
Overweight, n (%)	26 (8.41%)
Obese, n (%)	12 (3.88%)
Years since diagnosed with dysmenorrhea, if applicable (n=103), mean \pm SD	11.02 \pm 7.99
Number of the last three menstrual cycles accompanied by dysmenorrhea	
0, n (%)	15 (4.85%)
1, n (%)	31 (10.03%)
2, n (%)	43 (13.92%)
3, n (%)	220 (71.20%)
Number of weeks since last experienced dysmenorrhea, mean \pm SD	4.33 \pm 5.00; median 3.0; range 1.0–26.0
Number of days typically have menstrual bleeding during a normal menstrual cycle	6.60 \pm 5.10; median 5.0; range 0.0–33.0
Number of days experience dysmenorrhea per menstrual cycle, mean \pm SD	2.71 \pm 2.48; median 2.0; range 0.0–28.0
Level of dysmenorrhea pain (from “0” no pain to “10” the worst imaginable pain)	
Pain level during typical menstrual cycle, mean \pm SD	6.18 \pm 2.12
Pain level during most recent menstrual cycle, mean \pm SD	5.81 \pm 2.23
Number of times been pregnant	
0, n (%)	230 (74.43%)
1, n (%)	38 (12.30%)
2, n (%)	25 (8.09%)
3, n (%)	9 (2.91%)
\geq 4, n (%)	7 (2.27%)
Number of times given birth, if applicable (n=79)	
0, n (%)	25 (31.65%)
1, n (%)	31 (39.24%)
2, n (%)	19 (24.05%)
3, n (%)	4 (5.06%)
Ever seen a gynecologist, n (%)	251 (81.23%)
Currently receiving treatment for dysmenorrhea (including over-the-counter)	
Yes, n (%)	151 (48.87%)
No, n (%)	158 (51.13%)
Treatments currently receiving for dysmenorrhea (n=151)	
Over-the-counter pain medications, n (%)	88 (58.28%)
Prescription pain medications, n (%)	43 (28.48%)
LEPs/low-dose oral contraceptives, n (%)	29 (19.21%)
Other type of dysmenorrhea treatments, n (%)	23 (15.23%)
Traditional Chinese medicine, n (%)	19 (12.58%)
Iron supplements, n (%)	7 (4.64%)
Sleeping pills, n (%)	3 (1.99%)
Other drugs, n (%)	3 (1.99%)
Progestins, n (%)	2 (1.32%)
Intrauterine system/device, n (%)	0 (0.00%)
Medium-dose hormonal combinations, n (%)	1 (0.66%)
I do not know/I cannot remember, n (%)	5 (3.31%)

(Continued)

Table 4 (Continued)

Variable	Total (N=309)
Treatments ever received for dysmenorrhea	
Over-the-counter pain medications, n (%)	169 (54.69%)
Prescription pain medications, n (%)	97 (31.39%)
LEPs/low-dose oral contraceptives, n (%)	75 (24.27%)
Traditional Chinese medicine, n (%)	68 (22.01%)
Other type of dysmenorrhea treatments, n (%)	66 (21.36%)
Iron supplements, n (%)	22 (7.12%)
Medium-dose hormonal combinations, n (%)	14 (4.53%)
Sleeping pills, n (%)	14 (4.53%)
Other drugs, n (%)	12 (3.88%)
Progestins, n (%)	7 (2.27%)
Intrauterine system/device, n (%)	1 (0.32%)
I do not know/I cannot remember, n (%)	35 (11.33%)

Abbreviations: BMI, body mass index; LEP, low-dose estrogen progestin; SD, standard deviation.

treated for dysmenorrhea (48.9%). The most commonly reported treatments ever received for dysmenorrhea were OTC (54.7%) and prescription pain medications (31.4%). The treatments least often reported were IUS (0.3%) and progestins (2.3%).

As depicted in Table 5, respondents reported being approximately half as efficient (mean=53.3%, SD=22.4) at work/school/household chores due to dysmenorrhea, compared with their level of efficiency on a normal day (ie, a day with 100% efficiency). Sizeable minorities of respondents indicated having missed (18.8%), reduced volume (22.3%), or reduced efficiency (36.9%) in work/school/household chores in the past 6 months. Among those who reported having missed work/school/household chores in the past 6 months, a median of 4.0 (range=1.0–60.0) days were missed. For those who reduced their work/school/household chores volume in the past 6 months, volume was reduced for a median of 6.0 (range=1.0–58.0) days. A median of 8.5 (range=1.0–60.0) days of reduced efficiency at work/school/household chores in the past 6 months was reported.

Patient preferences: total sample

Over the range of attributes and levels included in the survey, mode of administration (RI=49.8%) was the most strongly associated with treatment preference, followed by chance of irregular bleeding (RI=17.3%), chance of nausea (RI=13.8%), and chance of symptoms becoming “improved” (RI=10.1%). Risk of VTE (RI=5.8%), chance of weight gain (RI=2.4%), and reduction in bleeding after 6 months (RI=0.8%) were the most weakly associated with preference. This is further

Table 5 Work productivity for the full sample (N=309)

Variable	Total (N=309)
Missed work/school/household chores in past 6 months	
Yes, n (%)	58 (18.77%)
No, n (%)	251 (81.23%)
Missed work/school/household chores in past 3 months (n=58)	
Yes, n (%)	47 (81.03%)
No, n (%)	11 (18.97%)
Reduced work/school/household chores volume in past 6 months	
Yes, n (%)	69 (22.33%)
No, n (%)	240 (77.67%)
Reduced work/school/household chores volume in past 3 months (n=69)	
Yes, n (%)	65 (94.20%)
No, n (%)	4 (5.80%)
Reduced efficiency in work/school/household chores in past 6 months	
Yes, n (%)	114 (36.89%)
No, n (%)	195 (63.11%)
Reduced efficiency in work/school/household chores in past 3 months (n=114)	
Yes, n (%)	109 (95.61%)
No, n (%)	5 (4.39%)
Number of days missed from work/school/household chores in past 6 months (n=58), mean \pm SD	8.02 \pm 9.79; median 4.0; range 1.0–60.0
Number of days missed from work/school/household chores in past 3 months (n=47), mean \pm SD	5.49 \pm 6.22; median 3.0; range 1.0–35.0
Number of days reduced work/school/household chores volume in past 6 months (n=69), mean \pm SD	7.11 \pm 7.78; median 6.0; range 1.0–58.0
Number of days reduced work/school/household chores volume in past 3 months (n=65), mean \pm SD	3.98 \pm 3.00; median 3.0; range 1.0–15.0
Number of days reduced efficiency in work/school/household chores in past 6 months (n=114), mean \pm SD	10.61 \pm 9.06; median 8.5; range 1.0–60.0
Number of days reduced efficiency in work/school/household chores in past 3 months (n=109), mean \pm SD	5.72 \pm 5.07; median 3.0; range 1.0–30.0
Percentage level of efficiency at work/school/household chores due to dysmenorrhea, compared to normal day, mean \pm SD	53.29 \pm 22.43

Note: In those cases in which data were based upon less than the full sample of N=309, the relevant sample size is provided in parentheses.

Abbreviation: SD, standard deviation.

illustrated in the RI weights shown in Figure 2. The preference weights and their 95% confidence intervals are also displayed in Figure 3. The greater the vertical changes evidenced within an attribute (as illustrated for mode of administration and chance of irregular bleeding), the stronger the relationship between that attribute and treatment choice.

The hierarchical Bayesian logistic regression model results are reported in Table 6. All levels of all attributes were nominally significantly associated with choice ($p < 0.05$ for all). Respondents had nominally significantly higher odds of preferring oral treatments: for twice-daily regimen, OR=4.90; for once-daily fixed cyclic regimen, OR=4.20; and for once-daily flexible extended regimen, OR=2.44; whereas for IUS, OR=0.02 (the reference group was the mean level of the attribute; $p < 0.001$ for all).

Patient preferences: prior hormonal therapy users

Among respondents with prior hormonal therapy use (n=85), the most common treatment ever received for dysmenorrhea was a low-dose hormonal combination (in Japan, for dysmenorrhea treatment, this refers only to LEPs/low-dose oral contraceptives; 88.2%). The same pattern of preference results was seen among the subset of women with prior hormonal therapy experience as was observed in the total sample. Specifically, mode of administration (RI=49.6%) was the most strongly associated with treatment preference, followed by chance of irregular bleeding (RI=17.7%), chance of nausea (RI=12.6%), and chance of symptoms becoming “improved” (RI=10.2%). Risk of VTE (RI=6.9%), chance of weight gain (RI=2.5%), and reduction in bleeding after 6 months (RI=0.5%) were the most weakly associated with preference (data not shown). All levels of all attributes were nominally significantly associated with choice ($p < 0.05$ for all), except for 35% chance of irregular bleeding, which was only marginally significant ($p = 0.096$). As with the total sample, respondents had nominally significantly higher odds of preferring orals: for twice-daily regimen, OR=4.20; for once-daily fixed cyclic regimen, OR=3.97; and for once-daily flexible extended regimen, OR=2.54; whereas for IUS, OR=0.02 (the reference group was the mean level of the attribute; $p < 0.001$ for all) (data not shown).

Discussion

The current study examined dysmenorrhea treatment preferences among a relatively broad range of women in Japan. The majority of participants did not have prior hormonal therapy experience and were not currently planning on becoming pregnant. By including respondents who self-reported having a dysmenorrhea diagnosis or experiencing symptoms of dysmenorrhea, as well as those who were not anticipating pregnancy (and were therefore presumably open to contraceptive treatment options), the sample was selected

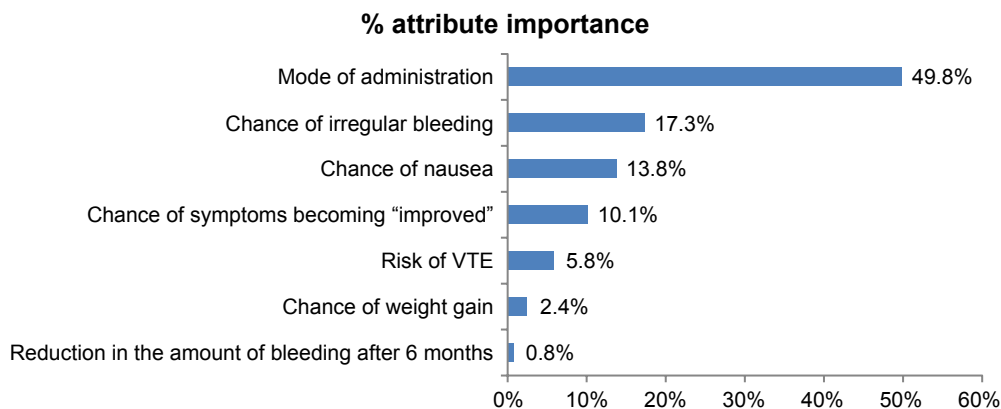


Figure 2 Relative importance of treatment attributes for the full study sample (N=309).
Abbreviation: VTE, venous thromboembolism.

to represent those who could seriously consider initiating the types of treatment options presented, as opposed to those for whom these options (and their corresponding preferences) might be irrelevant. This approach helped to enhance the ecological validity of our results.

In summary, results revealed that mode of administration factored heavily in dysmenorrhea treatment preferences. Specifically, women of reproductive age significantly preferred oral medications, with preferences being highest for

twice-daily (no menstrual bleeding occurs during administration of the drug) and once-daily fixed cyclic regimens (with 7 days of pill break; no menstrual bleeding occurs during administration of the drug, but starts during a pill break). These findings suggest that women with dysmenorrhea may prefer regular, simple treatment regimens. These preferences may have important implications not only for treatment decision making but also for treatment adherence in the real world, as a prior study has shown that risks for nonadherence

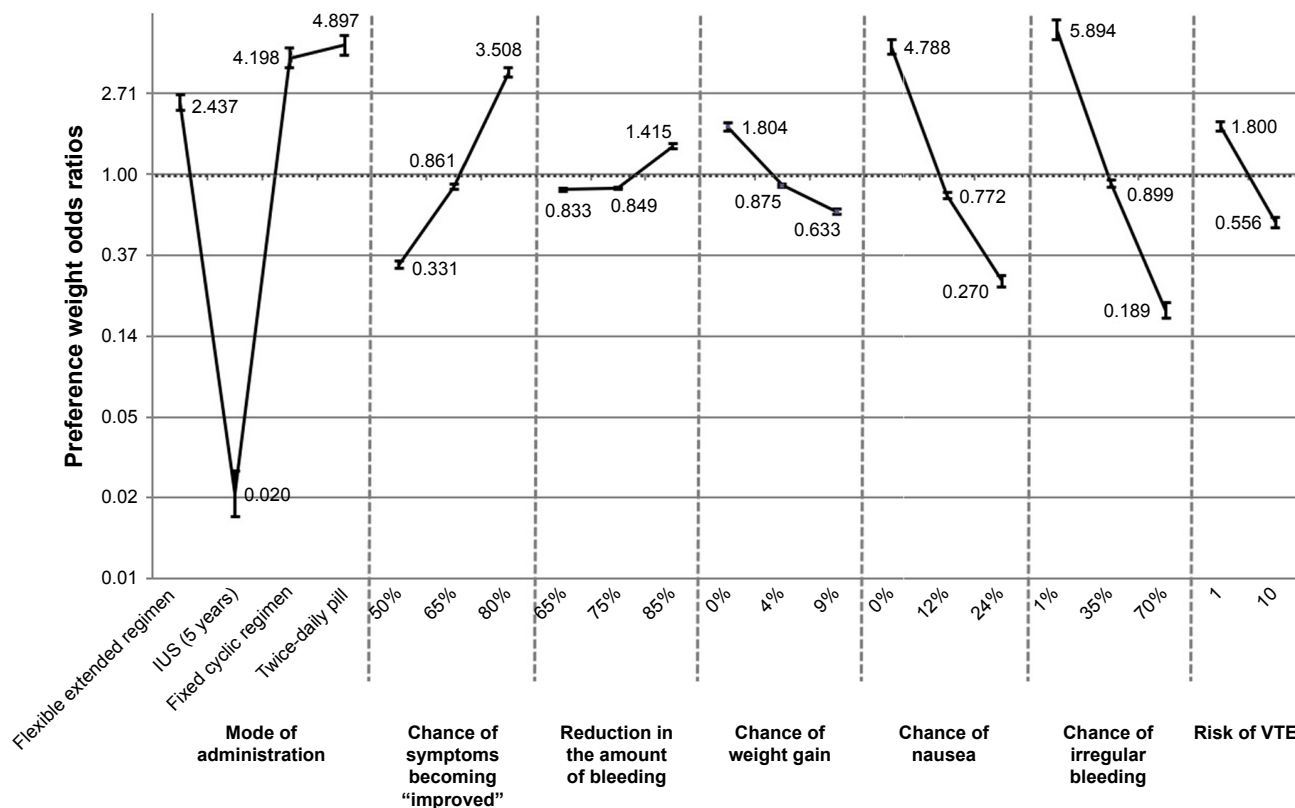


Figure 3 Patient preference weights exponentiated, with 95% confidence intervals (N=309).
Abbreviations: IUS, intrauterine system; VTE, venous thromboembolism.

Table 6 Regression model results predicting medication choice for the full study sample (N=309)

Attribute	Levels	b	SE	Z	p-value	OR
Mode of administration	Hormonal therapy with extended regimen (maximum 120 days)	0.89	0.05	18.16	<0.001	2.437
	Intrauterine device, long-term hormonal therapy which lasts for 5 years; do not have to be taken daily	-3.91	0.14	-27.32	<0.001	0.020
	Hormonal therapy with a fixed cyclic regimen	1.43	0.06	22.43	<0.001	4.198
	Hormonal therapy: twice-daily pill	1.59	0.06	26.05	<0.001	4.897
Chance of symptoms becoming "improved"	50% of women experiencing "improved" symptoms	-1.11	0.02	-44.59	<0.001	0.331
	65% of women experiencing "improved" symptoms	-0.15	0.02	-9.04	<0.001	0.861
	80% of women experiencing "improved" symptoms	1.26	0.03	41.41	<0.001	3.508
Reduction in the amount of bleeding after 6 months	65% of women experiencing less bleeding	-0.18	0.01	-22.51	<0.001	0.833
	75% of women experiencing less bleeding	-0.16	0.01	-21.55	<0.001	0.849
	85% of women experiencing less bleeding	0.35	0.02	22.07	<0.001	1.415
Chance of nausea	0% of women experiencing nausea	1.57	0.05	34.33	<0.001	4.788
	12% of women experiencing nausea	-0.26	0.02	-13.66	<0.001	0.772
	24% of women experiencing nausea	-1.31	0.04	-35.29	<0.001	0.270
Chance of weight gain	0% of women experiencing weight gain	0.59	0.02	23.82	<0.001	1.804
	4% of women experiencing weight gain	-0.13	0.01	-12.45	<0.001	0.875
	9% of women experiencing weight gain	-0.46	0.02	-25.59	<0.001	0.633
Chance of irregular bleeding	1% of women experiencing irregular bleeding	1.77	0.06	28.56	<0.001	5.894
	35% of women experiencing irregular bleeding	-0.11	0.02	-4.39	<0.001	0.899
	70% of women experiencing irregular bleeding	-1.67	0.05	-33.84	<0.001	0.189
Risk of VTE	About one case of VTE will occur among 10,000 women over an average of 1 year	0.59	0.03	19.97	<0.001	1.800
	About 10 cases of VTE will occur among 10,000 women over an average of 1 year	-0.59	0.03	-19.97	<0.001	0.556

Notes: ORs reflect the relative odds of selecting a given level within an attribute vs the mean level for that attribute. *b*: point estimates of part-worth utilities.

Abbreviations: OR, odds ratio; SE, standard error; VTE, venous thromboembolism.

and discontinuation may increase if prescribed medications are misaligned with patient preferences.²⁶

Chance of irregular bleeding and chance of nausea were also shown to be important factors for patient preference. It would be prudent for clinicians to take these findings into account when discussing treatment options with patients. In particular, nausea is commonly experienced by those with dysmenorrhea,¹⁴ and irregular bleeding has been cited as a reason why some women choose to discontinue treatment with COCs.³⁰ Results also demonstrated that risk of VTE was weakly associated with patient preference. While the link between estrogen-containing COCs and VTE has been well established,³¹ it is unclear whether patients are aware of the potential risk. A disconnect between patient preference and risk of VTE may present an opportunity for health care providers to further educate their patients on this issue, which can help to ensure patients make informed decisions.

The same results were replicated with a small subsample of women with prior hormonal therapy experience (n=85, data not shown), although few (1.2%) had ever used an IUS. The findings from these supplementary analyses suggest that preferences are not altered noticeably, given the experience. Thus, these analyses provided greater confidence in the initial

pattern of findings, as previous experience with hormonal therapy could be reasonably excluded as an alternative explanation.

Ultimately, dysmenorrhea largely goes undiagnosed and untreated, despite the substantial humanistic and economic burden attributed to this condition.^{14,24} Improving dysmenorrhea management will be essential to addressing this burden, given treatment is associated with better health-related quality of life and indirect cost savings.⁵ A prior meta-analysis of clinical trial data across multiple disease conditions demonstrated that the alignment of treatment with patient preference was related to higher treatment satisfaction, a greater likelihood of treatment completion, and better clinical outcomes.³² Therefore, patient preferences will play an integral role in devising strategies to enhance dysmenorrhea management.

Research suggests that women often inaccurately believe menstrual pain is normal, and as a result, may subsequently forgo treatment.^{5,14,24} However, those women who do receive treatment tend to be satisfied. For example, a systematic review reported that satisfaction was high for COCs with an extended or continuous regimen, although there was also evidence indicating some users discontinued treatment due to irregular bleeding.³⁰ A prospective longitudinal observational

study reported that a pill containing estradiol valerate and dienogest was associated with better outcomes (eg, shorter period, less bleeding, and less menstrual pain) and higher user satisfaction than a progestogen-only pill, with discontinuation rates of 20% and 26%, respectively.³³ A systematic review of research on levonorgestrel-releasing IUS found that over three-quarters of users reported symptom improvement and were satisfied with treatment.²³ Of direct relevance to satisfaction, the current study is one of the first to provide results on the treatment preferences of women with dysmenorrhea. Collectively, data on patient preferences for dysmenorrhea treatments will be vital in fostering greater physician–patient communication about treatment decision making, which can help to optimize treatment.

Limitations

There are several forms of selection bias, which are acknowledged but unavoidable. For example, it is quite possible that the patients included in this study were healthier or had better functioning compared with other dysmenorrhea patients. Additionally, the study was limited to internet users, and women without access to either the internet or the patient panels were not represented. These factors could have been confounded with treatment preferences. Furthermore, the study task was a simplified representation of a potential real-world choice among dysmenorrhea treatments. These choices were intended to simulate possible treatment decisions, but obviously they would not have the same clinical, financial, or emotional consequences of actual decisions that may be affected by preferences. Moreover, there are a multitude of other factors (eg, presentation of treatment options by a physician, internet search, family/friend opinion, etc) that would be present in a real-world choice selection that could not be reasonably accounted for in our controlled study. As a result, preferences, when patients are confronted with a real choice, may differ from our DCE results. However, potential hypothetical bias was limited as much as possible by constructing choice questions that mimicked realistic clinical choices and were consistent with prior research evidence. Although not central to the research questions, a few of our potential covariates (eg, comorbidities) were self-reported by respondents without clinical verification, thereby potentially introducing additional measurement error into the assessment of these variables.

Due to sample selection during recruitment, the results may not be generalizable to the entire dysmenorrhea population. By using age-based quotas and selecting patients from different geographic locations, we attempted to provide a

sample that was representative of patients with dysmenorrhea in Japan. However, no specific sampling frame was imposed, and we could not control the precise ratio of subgroups that may appear in the dysmenorrhea population.

Respondents' demographic characteristics and health history were reported, which allowed for these factors to be compared with other studies to better ascertain the representativeness of the sample and the generalizability of the findings. The age distribution in the current study was highly similar to other cross-sectional survey studies on dysmenorrhea in Japan.^{5–7,15} A larger proportion of participants in this study were employed (full time, part time, or self-employed) than in the two studies that reported on this variable,^{5,6} although the annual household income distribution in the current study was in line with a study by Tanaka et al.⁵ Most participants in this study had normal BMI, whereas the majority of participants in a study by Nohara et al were underweight.⁷ Additionally, OTC analgesic use in this study was moderately higher than that of outpatients, as well as women in the general population, with dysmenorrhea in studies by Tanaka et al,^{5,6} yet much lower than the OTC analgesic use reported by women with dysmenorrhea who did not seek medical treatment.⁵ Hence, in general, participant demographics in the present study were fairly comparable to those reported in other studies, which provides some support for the representativeness of the sample. Nevertheless, appropriate caution should be exercised in generalizing the findings more broadly, given there were modest differences between studies in sample health characteristics and treatment use.

Conclusion

Mode of administration factored heavily in dysmenorrhea treatment preferences; Japanese women of reproductive age significantly preferred oral treatments, with preferences being highest for twice-daily and once-daily fixed cyclic regimens. The most important factors driving preferences were the chance of irregular bleeding and the chance of nausea.

These findings help illuminate the perspective of women with dysmenorrhea, which can, in turn, help inform physician–patient communication and treatment decision making. It is important for physicians to provide patients with an explanation about dysmenorrhea treatments and to consider factors that may influence patient preference to ensure greater treatment acceptance and adherence.

Data sharing statement

Availability of the data underlying this publication will be determined according to Bayer's commitment to the

EFPIA/PhRMA “Principles for responsible clinical trial data sharing”. This pertains to scope, time point, and process of data access. As such, Bayer commits to sharing upon request from qualified scientific and medical researchers patient-level clinical trial data, study-level clinical trial data, and protocols from clinical trials in patients for medicines and indications approved in the US and European Union (EU) as necessary for conducting legitimate research. This applies to data on new medicines and indications that have been approved by the EU and US regulatory agencies on or after January 1, 2014.

Interested researchers can use www.clinicalstudydatarequest.com to request access to available datasets and supporting documents from clinical studies to conduct further research that can help advance medical science or improve patient care. Information on the Bayer criteria for listing studies and other relevant information is provided in the “Study sponsors” section of the portal. Data access will be granted to available datasets, protocols, and clinical study reports after approval by an independent scientific review panel. Bayer is not involved in the decisions made by the independent review panel. Bayer will take all necessary measures to ensure that patient privacy is safeguarded.

Abbreviations

BMI, body mass index; COC, combined oral contraceptive; DCE, discrete choice experiment; IUS, intrauterine system; LEP, low-dose estrogen progestin; MSS, mean sum of squares; NSAID, nonsteroidal anti-inflammatory drug; OR, odds ratio; OTC, over-the-counter; RI, relative importance; SAS, Statistical Analysis System; SD, standard deviation; VTE, venous thromboembolism.

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Author contributions

Tasuku Harada, Tetsushi Komori, and Sayako Akiyama contributed to study and survey design, reporting, and manuscript writing. Amir Goren and Enrique Basurto contributed to study and survey design, analysis, reporting, and manuscript writing. All authors contributed to interpretation of data,

critical revision of the paper and final approval of the version to be published, and all authors agree to be accountable for all aspects of the work.

Disclosure

Sayako Akiyama and Tetsushi Komori are employees of Bayer Yakuhin, Ltd. Tasuku Harada is a paid medical advisor to Bayer Yakuhin, Ltd. for the study and outside of the study. He has received funding from Fuji Pharma Co., Ltd., Mochida Pharmaceutical Co., Ltd., Nippon Shinyaku Co., Ltd., and Nobelpharma Co., Ltd., outside of the study. Amir Goren and Enrique Basurto were employees of Kantar Health at the time of the study and conducted the study with funding from Bayer Yakuhin, Ltd. The authors report no other conflicts of interest in this work.

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