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Preference-Based Assessments

Patient Preferences for Endometriosis Pain Treatments in the United States

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ABSTRACT

Objectives: To quantify patient preferences for endometriosis-associated pain treatments and risk tolerance in exchange for pain reduction and to explore whether preferences vary on the basis of patient characteristics.

Methods: US women with a self-reported physician diagnosis of endometriosis and moderate to severe dysmenorrhea and nonmenstrual pelvic pain (NMPP) completed an online discrete choice experiment survey. Each choice question had a pair of hypothetical treatments characterized by attributes with varying levels: improvements in severe dysmenorrhea, severe NMPP, and severe dyspareunia; mode of administration; and treatment-related risks of pregnancy-related problems, bone fracture later in life, and moderate to severe hot flashes. A random-parameters logit model was used to quantify preferences and the attributes' conditional relative importance.

Results: A total of 250 women (mean age 34 years) completed the survey. The conditional relative importance of attributes was 3.66 for risk of moderate to severe hot flashes among respondents with and 3.58 among respondents without experience with moderate to severe hot flashes; 1.70, 1.49, and 1.48 for improvements in dyspareunia, NMPP, and dysmenorrhea, respectively; 0.60 for risk of pregnancy-related problems; 0.53 for mode of administration; and 0.49 for bone fracture risk. Preference weights for bone fracture risk levels were not statistically significantly different. In exchange for a greater improvement in dysmenorrhea from severe to mild (vs moderate), respondents without a history of hot flashes accepted a greater increase in the risk of moderate to severe hot flashes (38%) than did respondents with this history (16%).

Conclusions: Respondents placed the greatest weight on risk of hot flashes, followed by improvements in dyspareunia, NMPP, dysmenorrhea. Bone fracture risk did not drive preferences.

Keywords: benefit-risk preferences, discrete choice, dysmenorrhea, dyspareunia, endometriosis, maximum acceptable risk, nonmenstrual pelvic pain, patient preferences, risk tolerance

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Introduction

Endometriosis is a heterogeneous disease affecting 6% to 10% women of reproductive age with variable symptoms including dysmenorrhea, nonmenstrual pelvic pain (NMPP), dyspareunia, infertility, and painful bowel and/or bladder symptoms, among other symptoms.[1–3] Endometriosis has a negative effect on health-related quality of life and may impair work productivity and daily activities, affect intimate relationships and family planning, and impact emotional well-being.[4,5] The economic burden associated with endometriosis is also significant, with surgery-related hospitalizations being a key driver of direct costs.[6–10]

Various surgical and medical options are used to treat pain associated with endometriosis. Medical treatments include nonsteroidal anti-inflammatory drugs, narcotics, hormonal contraceptives, progestin therapy, gonadotropin-releasing hormone (GnRH) analogs (eg, leuprolide, goserelin, and nafarelin), and danazol. Of these, the GnRH agonists, danazol, and injectable progestin are approved by the US Food and Drug Administration for the treatment of endometriosis[11]; the other treatments are used

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Table 1. Attributes and levels for the discrete choice experiment

Attribute	Levels	
Improvement in dysmenorrhea	• Severe to no pain • Severe to mild pain • Severe to moderate pain	
Improvement in nonmenstrual pelvic pain	• Severe to no pain • Severe to mild pain • Severe to moderate pain	
Improvement in dyspareunia	• Severe to mild pain • Severe to moderate pain • No change to severe pain	
Mode and frequency of administration	• Pill or tablet every day • Injection once per month or once every several months	
Increased risk of pregnancy-related problem if pregnancy occurs during treatment	• Unknown risk • Known risk: 0 out of 100 women who become pregnant will have pregnancy-related problem (0%) • Known risk: 2 out of 100 women who become pregnant will have pregnancy-related problem (2%) • Known risk: 7 out of 100 women who become pregnant will have pregnancy-related problem (7%)	
Increased risk of bone fracture later in life	• Unknown risk • Known risk: 0 out of 100 women (0%) • Known risk: 2 out of 100 women (2%) • Known risk: 5 out of 100 women (5%) • Known risk: 10 out of 100 women (10%)	
Increased risk of moderate to severe hot flashes while on treatment*	Narrow range • Known risk: 0 out of 100 women (0%) • Known risk: 30 out of 100 women (30%) • Known risk: 50 out of 100 women (50%) • Known risk: 65 out of 100 women (65%)	Wide range • Known risk: 0 out of 100 women (0%) • Known risk: 30 out of 100 women (30%) • Known risk: 50 out of 100 women (50%) • Known risk: 85 out of 100 women (85%)

*The study included an internal validity test of respondents' sensitivity to absolute differences in the additional risk of moderate to severe hot flashes, known as a scope test. To implement the scope test, respondents were randomly assigned to 1 of 2 ranges of risk: narrow (0%-65%) or wide (0%-85%).

off label. Current treatments vary in terms of effectiveness, modes of administration, tolerability, and side-effects profile. For example, GnRH analogs often cause hot flashes and decreased bone mineral density and must be administered by injection or intranasally.[12,13] Danazol may cause androgenic side effects such as hirsutism and voice changes,[14,15] whereas injectable progestins may cause abnormal uterine bleeding, mood problems, and weight changes.[16] Many women do not experience sufficient or sustained relief from endometriosis pain with the currently available treatment options.[17] Given the limited effectiveness of available treatments, a significant number of patients with endometriosis pain resort to use of opioid to manage their pain—a concerning practice in light of the opioid epidemic.

There is emerging interest in the conduct of patient preference studies to inform benefit-risk decision making for new products. Specifically, the US Food and Drug Administration plans to incorporate patient experience data into its structured benefit-risk assessment, as part of the Prescription Drug User Fee Act VI and the 21st Century Cures Act commitments.[18,19] Patients can provide unique perspectives about what treatments should be available, which may differ from the perspectives of regulators, healthcare providers, and medicinal product manufacturers. Given the limitation with current treatment options, endometriosis was considered an important condition in which to explore patient perspectives on treatment.

The primary objective of this study was to quantify preferences for attributes of treatments for endometriosis-associated pain among women with endometriosis in the United States. Additional objectives were to examine tolerance for treatment-related risks in exchange for specific reductions in pain and to explore whether preferences for selected treatment attributes vary on the basis of patient characteristics. We developed a discrete choice experiment (DCE) survey to address these objectives.

Methods

Survey Instrument

We developed a DCE survey instrument to elicit respondents' preferences for select attributes of treatments for endometriosis-related pain.[20] The survey instrument also included questions about patient demographic characteristics, treatment experience, and health history.

In each of a series of DCE questions, respondents chose the most preferred profile from a pair of hypothetical treatment profiles. Each hypothetical profile was defined by attributes with varying levels. Respondents' choices depended on the relative importance patients place on the attribute levels. Attribute selection and descriptions were informed by input from clinical experts, product labels (prescribing information), and endpoints from endometriosis clinical trials. Attributes and levels were selected to include the range of clinically relevant endpoints for comparability with currently available treatment profiles as well as risk levels that respondents may be willing to accept (see Table 1).

The benefit (efficacy) attributes, on the basis of the endometriosis daily pain impact diary items,[21] consisted of improvements in 3 types of endometriosis-related pain: dysmenorrhea, NMPP,

Figure 1. Example of discrete choice experiment question.

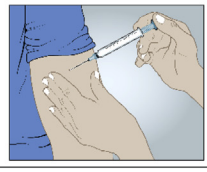
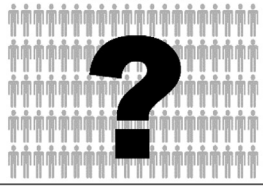
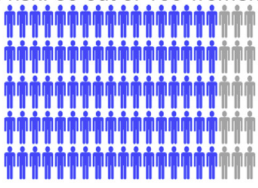
Medicine Feature	Medicine A	Medicine B
Improvement in pelvic pain during your period	Severe to moderate pain No pain Mild Moderate Severe	Severe to mild pain No pain Mild Moderate Severe
Improvement in pelvic pain when you are not having your period	Severe to moderate pain No pain Mild Moderate Severe	Severe to mild pain No pain Mild Moderate Severe
Improvement in pain during and/or after sexual intercourse	Severe to mild pain No pain Mild Moderate Severe	No change Severe pain
How you take the medicine	Pill or tablet every day 	Injection once per month or once every several months 
Risk of pregnancy-related problem if pregnancy occurs during treatment	Known risk: 2 out of 100 women who become pregnant while taking the medicine will have pregnancy-related problem (2%) 	Known risk: 0 out of 100 women who become pregnant while taking the medicine will have pregnancy-related problem (0%) 
Increased risk of bone fracture later in life	Known risk: 5 out of 100 women (5%) 	Unknown risk 
Risk of moderate to severe hot flashes while on treatment	Known risk: 85 out of 100 women (85%) 	Known risk: 30 out of 100 women (30%) 
Which medicine would you choose if these were the only two medicines available?	☐	☐

Table 2. Characteristics of participants in the pretest interviews.

Question	Respondents (N = 15)
Age (y), mean ± SD	40 ± 6
Marital status	
Single/never married	1
Married/living as married/civil partnership	13
Divorced or separated	1
Widowed/surviving partner	0
Other	0
Highest level of education	
Less than high school	0
Some high school	1
High school or equivalent (eg, GED)	0
Some college but no degree	2
Technical school	1
Associate's degree (2-y college degree)	2
4-y college degree (eg, BA and BS)	4
Some graduate school but no degree	0
Graduate or professional degree (eg, MBA, MS, MD, and PhD)	5
Employment status*	
Employed full-time	7
Employed part-time	1
Self-employed	1
Homemaker	3
Student	1
Retired	0
Disabled/unable to work	2
On medical leave of absence from work	0
Unemployed but looking for work	2
Unemployed and not looking for work	0
Insurance type	
I do not have health insurance	0
Private insurance that I pay for myself	4
Private insurance that my or my spouse's employer pays all or part of	9
Medicaid	3
Medicare	0
Veterans health insurance	0
Other	0
Don't know	0
Duration of symptoms before diagnosis, mean (SD)	4 (4)
<1 y	2
1-5 y	4
6-10 y	3
>10 y	2
Years since diagnosis, mean (SD)	10 (8)
<1 y	0
1-5 y	1
6-10 y	0
>10 y	4
Worst level of dysmenorrhea in the last 6 mo	
No pain	0
Mild pain, but you are able to do the things you usually do	0
Moderate pain, and you may have some difficulty doing the things you usually do	4
Severe pain, and you may have great difficulty doing the things you usually do	10
Not asked/did not answer	1
Worst level of nonmenstrual pelvic pain in the last 6 mo	
No pain	0
Mild pain, but you are able to do the things you usually do	3
Moderate pain, and you may have some difficulty doing the things you usually do	8
Severe pain, and you may have great difficulty doing the things you usually do	4
Worst level of dyspareunia in the last 6 mo	
No pain	1
Mild discomfort or pain that you can tolerate	4
Moderate discomfort or pain that will cause you to stop sexual intercourse	7
Severe pain that makes you avoid engaging in sexual intercourse	2
Not applicable: I was not sexually active for reasons other than my endometriosis or did not have sexual intercourse	1
Ever had severe dysmenorrhea†	
Yes	2
No	0
Not asked/did not answer	13
Ever had severe nonmenstrual pelvic pain†	
Yes	4
No	0
Not asked/did not answer	11
Ever had severe dyspareunia†	
Yes	3
No	2
Not asked/did not answer	10
Previous surgical treatments for endometriosis-related pain	
Laparoscopy	10
Laparotomy	2
None of the above	4
Endometriosis diagnosed using laparoscopy or laparotomy	
Yes	7
No	8
Endometriosis diagnosis confirmed using laparoscopy or laparotomy‡	
Yes	2
No	2
Not asked/did not answer	11
Medications ever taken to treat endometriosis-related pain‡	
Yes	9
No	0
Ibuprofen (eg, Advil and Motrin)	4
Naproxen (eg, Aleve)	3
Acetaminophen (eg, Tylenol)	6
Narcotics (eg, Percocet, Vicodin, OxyContin, and Codeine)	4
Hormonal contraceptives such as birth control pills, patches, or vaginal rings	5
Progestin therapy such as an intrauterine device (Mirena), contraceptive implant, or contraceptive injection (Depo-Provera)	1
Lupron	1
Danazol/Danocrine	0
Other prescription pain medicines	3
Other medicines	3
I have never taken any of these medicines to treat endometriosis-related pain	0

continued

continued on next page

Table 2. Continued

Question	Respondents (N = 15)
Medications taken in the last 6 mo to treat endometriosis-related pain‡	
Yes	9
No	0
Ibuprofen (eg, Advil and Motrin)	4
Naproxen (eg, Aleve)	3
Acetaminophen (eg, Tylenol)	5
Narcotics (eg, Percocet, Vicodin, OxyContin, and Codeine)	2
Hormonal contraceptives such as birth control pills, patches, or vaginal rings	1
Progestin therapy such as an intrauterine device (Mirena), contraceptive implant, or contraceptive injection (Depo-Provera)	1
Lupron	0
Danazol/Danocrine	0
Other prescription pain medicines	0
Other medicines	2
I have not taken any of these medicines to treat endometriosis-related pain in the last 6 mo	0
Effectiveness of current medication for endometriosis-related pain (scale: 1 = not effective; 7 = very effective), mean ± SD	3 ± 1
Importance that a medication for endometriosis-related pain may reduce the use of opioid medicines (scale: 1 = not important; 7 = very important), mean ± SD	6 ± 2
Among respondents with children, family planning goals‡	
I hope to get pregnant and have more children	0
I hope to expand my family by adopting a child(ren)	0
I have not decided whether I want to have more children	1
I do not plan to have or to adopt any more children	10
Not asked/did not answer	4
Among respondents with no children, family planning goals‡	
I hope to get pregnant and have children	2
I hope to adopt children	0
I have not decided whether I want to have children	0
I do not plan to have any children	2
Not asked/did not answer	11
Personal history of bone problems	
Yes	2
No	9
Not asked/did not answer	4
Family history of bone problems	
Yes	7
No	4
Do not know	0
Not asked/did not answer	4
Previous experience with moderate to severe hot flashes	
Yes	7
No	4
Not asked/did not answer	4

GED indicates general educational diploma; SD, standard deviation.
*One respondent selected 3 categories.
†Question was added after the first day of interviews.
‡Respondents could select 1 or more responses.

and dyspareunia (see Appendix A in Supplemental Materials found at https://doi.org/10.1016/j.jval.2018.12.010). Three risk attributes were evaluated: risk of pregnancy-related problems (which was conditional on becoming pregnant and thus avoidable), risk of bone fracture above the background rate (which was latent and would be experienced in the future), and risk of moderate to severe hot flashes (which was contemporaneous). The attributes describing the risks of pregnancy-related problems and bone fracture each included an "unknown" risk level to explore respondents' preferences for uncertainty. An attribute evaluating the mode and frequency of administration was also included. Figure 1 presents an example of a DCE question.

Profiles and profile pairs were determined by a D-optimal fractional factorial experimental design, which was created in Sawtooth Software (Sawtooth Software Inc, Sequim, WA).[22–24] The experimental design consisted of combinations of the attribute levels that describe the full set of treatment profiles included in the survey, and the profile pairs in a series of choice tasks that allowed for the estimation of a unique preference weight for each attribute level. The objective of the experimental design was to develop a set of choice tasks that would provide as much preference information as possible to describe trade-offs among a given set of attributes and levels for a given sample size while limiting respondent burden. The experimental design consisted of 48 pairs of hypothetical treatment profiles, split into 6 blocks of 8 choice pairs.

When answering the choice questions, all respondents were asked to imagine a hypothetical reference condition, in which they have severe dysmenorrhea, severe NMPP, and severe dyspareunia. The reference condition defined hypothetical baseline symptoms before or without treatment, drawing on attribute definitions presented earlier in the survey. The intent was to ensure that changes due to treatment were exogenous and interpreted consistently across respondents and that the benefit attribute levels represented improvements for all respondents. The study also included an internal validity test of respondents' sensitivity to absolute differences in the additional risk of moderate to severe hot flashes, known as a scope test (see the Appendix in Supplemental Materials found at https://doi.org/10.1016/j.jval.2018.12.010).

A draft version of the survey instrument was pretested in semistructured interviews with a convenience sample of 15 individuals from the study population (Table 2). Key refinements to the survey instrument resulting from the pretest interviews included (1) clarifying the description of the reference condition to more clearly distinguish it from the respondent's actual condition; (2) expanding on the description of the mode of administration attribute to describe frequency of dosing; (3) asking respondents to report personal or family history of bone problems; (4) clarifying that the risk of bone fracture would be in addition to the respondent's baseline risk of bone fracture and delayed; (5) clarifying that hot flashes would occur 3 to 5 times per week; and (6) revising the screening question to ask about the worst level of pain in the last 6 months to make it easier for respondents with variable pain levels to answer the question.

Study Population

Survey respondents were eligible for the study if they were aged 18 to 49 years or older. The inclusion criterion for age initially was 18 years and older but was refined to 18 to 49 years after recruitment was initiated to limit the sample to individuals who were premenopausal. As a result, 1 respondent was older than 49 years. Eligibility criteria also required respondents to have self-

reported a physician diagnosis of endometriosis, experienced moderate or severe menstrual pain and NMPP in the last 6 months, taken medication for endometriosis-related pain in the last 6 months, not undergone hysterectomy or oophorectomy, not been pregnant at the time of the survey, and had a menstrual period in the last 6 months.

Respondents were recruited through 2 sources. The Endometriosis Association sent email invitations to its members to be screened for survey eligibility (in April-May 2017), and Survey Sampling International (SSI) recruited patients with endometriosis through a patient panel website (in November 2017). For respondents recruited through the Endometriosis Association, a $25 donation was made to the Endometriosis Association for every completed survey, whereas SSI web panelists who completed the survey received panel points with an approximate cash value of $6 to $8. All respondents provided informed consent electronically before completing the survey. The survey was granted an exemption from review by the institutional review board of RTI International.

Statistical Analyses

The analysis sample excluded respondents who did not answer at least 1 choice question, did not vary their answers for the choice questions (selecting only medicine A or only medicine B), and completed the survey in 6 minutes or less, assuming that these respondents may not have provided meaningful responses to the choice questions. Statistical analyses, including the summary of descriptive statistics, the analyses of the DCE choice data (including a scope test analysis), subgroup analyses, and calculation of maximum acceptable risk (MAR), were performed with NLOGIT (Econometric Software Inc, Plainview, NY).[25]

A random-parameters logit (RPL) regression model was used to analyze the choice data collected in this DCE. RPL estimates a preference weight for each attribute level, accounts for the panel nature of the data, and accounts for unobserved differences in preferences across respondents (preference heterogeneity).[26,27] All variables in the final models were effects-coded, which allowed the estimation of 1 parameter for each attribute level without imposing any functional form on the effect that attribute levels have on the relative preferences for treatments.

Subgroup analyses examined whether preferences differed systematically on the basis of patient characteristics. Mutually exclusive subgroups were identified on the basis of respondents' experience with moderate to severe hot flashes, interest in becoming pregnant, personal or family history of bone problems, age, and experience with and interest in reducing opioid use to treat endometriosis-related pain. For each subgroup analysis, a dummy variable was used, which was set equal to 1 if the respondent belonged to the subgroup and to 0 if the respondent did not belong to the subgroup. To examine whether an interest in becoming pregnant or whether a personal or family history of bone problems or previous experience with moderate to severe hot flashes influenced risk preferences, each of the dummy-coded indicator variables for these subgroups was interacted only with the independent variables describing the corresponding risk attribute. To examine whether interest in reducing the use of opioids, experience with the use of opioids, or respondent age influenced preferences for the treatment attributes, each of the dummy-coded indicator variables for opioid-related and age subgroups was interacted with all the independent variables describing the treatment attributes. The RPL parameter estimates for the interaction terms were interpreted as preference-weight adjustments that applied only to respondents in the corresponding subgroup. A χ^2 test of the joint significance of the interaction terms indicated whether preferences between the groups were statistically significantly different (ie, jointly different from 0).

The log-odds relative preference weights (RPL parameter estimates) were used to calculate the relative importance of attributes over the ranges of attribute levels included in the DCE (or conditional relative importance) and measures of risk tolerance. Conditional relative importance was calculated as the difference between the preference weight for the attribute level with the highest preference weight and the preference weight for the level of the same attribute with the lowest preference weight. This difference represents the maximum change in utility achievable with any attribute, conditional on the levels chosen for the attributes in the study. The mean MAR for treatment-related risks and the 95% confidence intervals (CIs) around these means were calculated using the RPL regression parameters from the subgroup model. The mean MAR in exchange for specific improvements in treatment benefit was calculated as the negative ratio of the relative importance of an improvement in treatment effectiveness (eg, the vertical distance between preference weights corresponding to different levels of improvement in endometriosis-associated pain), or an improvement in another treatment attribute, to the value of a unit change in the risk attribute (accounting for the fact that this might vary across different absolute levels of risk). The value of a unit change in the risk attribute was determined by the linear interpolation of the preference weight at the point at which the relative importance of an increase in the risk attribute is equal to the relative importance of an improvement in treatment effectiveness. In some cases, these calculations resulted in MAR estimates that were outside the risk ranges used in the study design. These results relied on linear extrapolation of preferences outside of the study range.

The results of the RPL model were used to examine respondents' views of unknown versus known risks. Using the RPL regression results, we calculated the mean MAR of risk attributes (and the 95% CIs around these means) that is equivalent to an unknown level of risk attributes. This MAR was calculated as the change in a risk that is exactly equivalent to the perceived disutility of an unknown risk.

Results

Respondent Population

Approximately 26 000 Endometriosis Association members were invited by email to be screened for survey eligibility; 1536 emails were opened. Of 360 individuals who accessed the survey link, 101 were eligible and consented to participate. Of the 733 panel members who were recruited by SSI and accessed the survey link, 183 were eligible and consented to participate. In total, 250 respondents were in the final sample: 89 from the Endometriosis Association and 161 from the SSI panel.

Table 3 presents respondents' demographic characteristics and experiences with endometriosis. Respondents' mean age was 33.7 ± 7.66 years; mean age at diagnosis was 22.3 ± 8.96 years, and mean duration of disease was 11.4 ± 8.33 years.

Severe menstrual pain and severe NMPP were experienced by 64.0% (n = 160) and 37.6% (n = 94) of respondents in the previous 6 months, respectively. Severe menstrual pain and NMPP were experienced at any time by 99.6% (n = 249) and 91.2% (n = 228) of respondents, respectively; 78.0% (n = 195) of respondents reported having experienced severe dyspareunia at any time. Personal or family history of bone problems was reported by 47.2% (n = 118) of respondents, and experience with moderate to severe hot flashes was reported by 51.2% (n = 128) of respondents. One-third (33.6%) of respondents were interested in becoming pregnant. In the

Table 3. Respondent characteristics.

Characteristic	All respondents (N = 250)
Age (y)	
N	250
Mean ± SD	33.7 ± 7.66
Median	34.0
Minimum, maximum	18, 53
Age at endometriosis diagnosis (y)	
N	250
Mean ± SD	22.3 ± 8.96
Median	22.0
Minimum, maximum	1, 49
Marital status	
n	250
Single/never married	90 (36.0%)
Married/living as married/civil partnership	138 (55.2%)
Divorced or separated	17 (6.8%)
Widowed/surviving partner	3 (1.2%)
Other	2 (0.8%)
Highest level of education	
n	250
Less than high school	2 (0.8%)
Some high school	4 (1.6%)
High school or equivalent (eg, GED)	29 (11.6%)
Some college but no degree	55 (22.0%)
Technical school	17 (6.8%)
Associate's degree (2-y college degree)	34 (13.6%)
4-y college degree (eg, BA and BS)	64 (25.6%)
Some graduate school but no degree	12 (4.8%)
Graduate or professional degree (eg, MBA, MS, MD, and PhD)	33 (13.2%)
Employment status	
n	250
Employed full-time	122 (48.8%)
Employed part-time	25 (10.0%)
Self-employed	18 (7.2%)
Homemaker	29 (11.6%)
Student	15 (6.0%)
Retired	1 (0.4%)
Disabled/unable to work	16 (6.4%)
On medical leave of absence from work	4 (1.6%)
Unemployed but looking for work	14 (5.6%)
Unemployed and not looking for work	6 (2.4%)
Insurance type*	
n	250
I do not have health insurance	23 (9.2%)
Private insurance that I pay for myself	54 (21.6%)
Private insurance that my or my spouse's employer pays all or part of	103 (41.2%)
Medicaid	34 (13.6%)
Medicare	16 (6.4%)
Veterans health insurance	5 (2.0%)
Other	19 (7.6%)
Do not know	3 (1.2%)
Duration of endometriosis symptoms before diagnosis	
n	250
<1 y	28 (11.2%)
1-5 y	126 (50.4%)
6-10 y	55 (22.0%)
>10 y	41 (16.4%)
Years since diagnosis	
n	250
Mean ± SD	11.4 ± 8.33
Median	10.0
Minimum, maximum	0, 40

continued

Table 3. Continued

Characteristic	All respondents (N = 250)
Worst level of dysmenorrhea in the last 6 mo	
n	250
No pain	0
Mild pain, but you are able to do the things you usually do	0
Moderate pain and you may have some difficulty doing the things you usually do	90 (36.0%)
Severe pain and you may have great difficulty doing the things you usually do	160 (64.0%)
Among respondents without severe dysmenorrhea in the last 6 mo, those who had ever had severe dysmenorrhea	
n	90
Has ever had severe dysmenorrhea	89 (98.9%)
Has never had severe dysmenorrhea	1 (1.1%)
Worst level of nonmenstrual pelvic pain in the last 6 mo	
n	250
No pain	0
Mild pain, but you are able to do the things you usually do	0
Moderate pain, and you may have some difficulty doing the things you usually do	156 (62.4%)
Severe pain, and you may have great difficulty doing the things you usually do	94 (37.6%)
Among respondents without severe nonmenstrual pelvic pain in the last 6 mo, those who had ever had severe nonmenstrual pelvic pain	
n	156
Has ever had severe nonmenstrual pelvic pain	134 (85.9%)
Has never had severe nonmenstrual pelvic pain	22 (14.1%)
Worst level of dyspareunia in the last 6 mo	
n	250
No pain	13 (5.2%)
Mild discomfort or pain that you can tolerate	60 (24.0%)
Moderate discomfort or pain that will cause you to stop sexual intercourse	87 (34.8%)
Severe pain that makes you avoid engaging in sexual intercourse	66 (26.4%)
Not applicable: I did not have sexual intercourse for reasons other than my endometriosis	24 (9.6%)
Among respondents without severe dyspareunia in the last 6 mo, those who had ever had severe dyspareunia	
n	184
Has ever had severe dyspareunia	129 (70.1%)
Has never had severe dyspareunia	55 (29.9%)
Previous surgical treatments for endometriosis-related pain*	
n	250
Laparoscopy	183 (73.2%)
Laparotomy	27 (10.8%)
None of the above	59 (23.6%)
Endometriosis diagnosed using laparoscopy or laparotomy	
n	250
Yes	181 (72.4%)
No	69 (27.6%)
Among respondents whose endometriosis was not diagnosed using laparoscopy or laparotomy, diagnosis was ever confirmed using laparoscopy or laparotomy	
n	69
Yes	18 (26.1%)
No	51 (73.9%)

continued on next page

Table 3. Continued

Characteristic	All respondents (N = 250)
Medications ever taken to treat endometriosis-related pain*	
n	250
Ibuprofen (eg, Advil and Motrin)	233 (93.2%)
Naproxen (eg, Aleve)	176 (70.4%)
Acetaminophen (eg, Tylenol)	203 (81.2%)
Narcotics (eg, Percocet, Vicodin, OxyContin, Codeine, and Norco)	144 (57.6%)
Hormonal contraceptives such as birth control pills, patches, or vaginal rings	178 (71.2%)
Progestin therapy such as an intrauterine device (Mirena), contraceptive implant, or Depo-Provera	79 (31.6%)
Lupron	59 (23.6%)
Danazol/Danocrine	9 (3.6%)
Other prescription pain medicines	45 (18.0%)
I have never taken any of these medicines to treat endometriosis-related pain	0
Medications taken in the last 6 mo to treat endometriosis-related pain*	
n	250
Ibuprofen (eg, Advil and Motrin)	194 (77.6%)
Naproxen (eg, Aleve)	113 (45.2%)
Acetaminophen (eg, Tylenol)	157 (62.8%)
Narcotics (eg, Percocet, Vicodin, OxyContin, Codeine, and Norco)	92 (36.8%)
Hormonal contraceptives such as birth control pills, patches, or vaginal rings	82 (32.8%)
Progestin therapy such as an intrauterine device (Mirena), contraceptive implant, or Depo-Provera	34 (13.6%)
Lupron	11 (4.4%)
Danazol/Danocrine	1 (0.4%)
Other prescription pain medicines	26 (10.4%)
I have never taken any of these medicines to treat endometriosis-related pain	0
Effectiveness of current medication for endometriosis-related pain (scale: 1 = not effective at all; 7 = extremely effective)	
n	249
Mean ± SD	3.8 ± 1.52
Median	4.0
Minimum, maximum	1, 7
Importance that a medication for endometriosis-related pain may reduce the use of opioid medicines (scale: 1 = not important at all; 7 = extremely important)	
n	250
Mean ± SD	5.9 ± 1.42
Median	7.0
Minimum, maximum	1, 7
Interest in becoming pregnant	
Yes	84 (33.6%)
No or missing	166 (66.4%)
Personal or family history of bone problems	
Yes	118 (47.2%)
No or missing	132 (52.8%)
Previous experience with moderate to severe hot flashes	
Yes	128 (51.2%)
No or missing	122 (48.8%)

GED indicates general educational diploma; SD, standard deviation.
*Respondents could select 1 or more responses.

previous 6 months, 36.8% of respondents had taken opioids for endometriosis pain and 57.6% of respondents had never taken opioids for endometriosis pain. On a scale of 1 to 7, respondents' mean rating of the effectiveness of their medication for endometriosis pain was 3.8 ± 1.52. For 72.4% (n = 181) of respondents, endometriosis had been diagnosed by laparoscopy or laparotomy. Of note, 76.4% (n = 191) of respondents reported having a surgical procedure (ie, laparoscopy, open surgery, or laparotomy) to treat their endometriosis pain.

Preference Weights

Subgroup analyses revealed that respondents with experience with moderate to severe hot flashes had systematically different preferences than the respondents without experience of moderate to severe hot flashes. There were no systematic differences in preferences between subgroups defined by an interest in becoming pregnant, a personal or family history of bone problems, age, or experience with using or interest in reducing opioids for endometriosis pain.

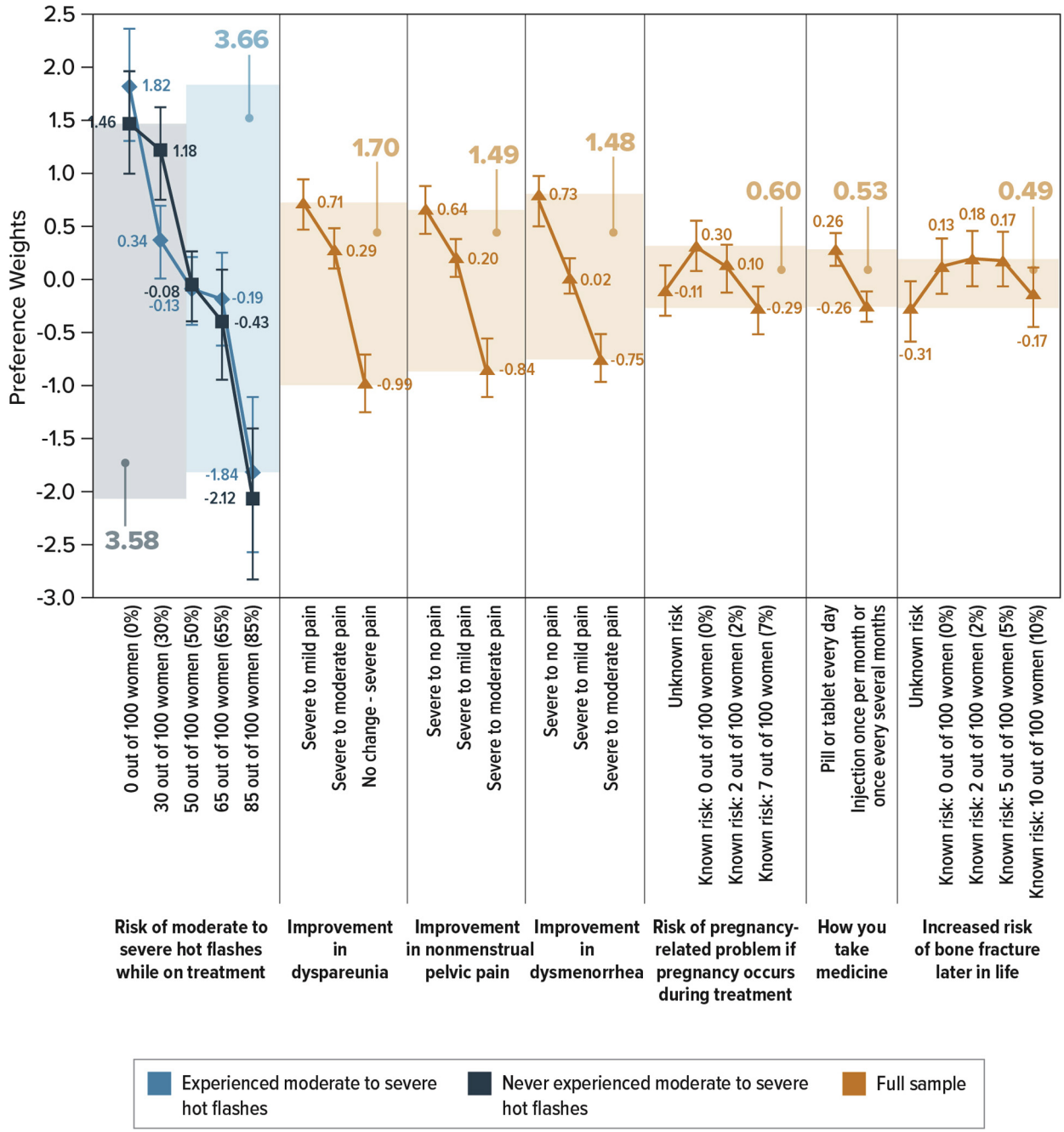
Figure 2 summarizes the mean parameter estimates from the RPL model, which included subgroups with and without experience with moderate to severe hot flashes. The estimated preference weights for most attributes were consistent with the natural ordering of the levels—that is, better outcomes or features were preferred to worse outcomes or features. For example, on average, respondents preferred treatments that reduce severe pain to mild pain more than treatments that reduce severe pain to moderate pain and preferred treatments with lower risks of pregnancy-related problems and moderate to severe hot flashes. Nevertheless, some of the preference weights for risks of bone fracture were disordered (ie, preference weights were greater for higher risks than for lower risks), although these disordered preference weights were not statistically significantly different from one another.

The vertical distance between preference weights represents the relative importance of moving from one level of an attribute to another level of the same attribute. In Figure 2, treatments that reduce severe levels of dysmenorrhea, NMPP, or dyspareunia to mild levels rather than moderate levels had relative importances of approximately 0.77 (= 0.02 − [−0.75]), 1.04 (= 0.20 − [−0.84]), and 0.42 (= 0.71 − 0.29), respectively. Therefore, this improvement in dysmenorrhea (severe to mild instead of severe to moderate) was 0.74 (= 0.77 ÷ [1.04]) times as important as the same improvement in NMPP, and 1.83 (= 0.77 ÷ [0.42]) times more important than the same improvement in dyspareunia.

Conditional Relative Importance

The preference weights in Figure 2 show that given the levels chosen for the attributes in the study, the additional risk of moderate to severe hot flashes was the most important attribute (conditional on the attributes and levels included in the study) to all respondents ($P<.050$). This attribute had the largest difference between the largest and smallest preference weights (3.66 [95% CI 2.51-4.81] among respondents who had experienced moderate to severe hot flashes and 3.58 [95% CI 2.50-4.66] among respondents who had not). In comparison, the conditional relative importances of the various types of endometriosis-related pain were all similar to one another ($P>.050$): dyspareunia, 1.70 (95% CI 1.20-2.20); NMPP, 1.49 (95% CI 1.01-1.97); and dysmenorrhea, 1.48 (95% CI 1.04-1.92). The relative importance of the risk of pregnancy-related problems was 0.60 (95% CI 0.20-1.00), of mode of administration was 0.53 (95% CI 0.22-0.83), and of risk of bone fracture was 0.49 (95% CI 0.09-0.90) ($P>.050$).

Figure 2. Relative preference weights for treatment attributes. The vertical bars surrounding each mean preference weight denote the 95% confidence interval about the point estimate.



Risk-Tolerance Measures

The MARs of pregnancy-related problems, bone fracture, and moderate to severe hot flashes (and the corresponding 95% CIs) were calculated for all possible changes between levels of efficacy and mode of administration (see Table 4; see also Appendix Table C-1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2018.12.010).

For an improvement in dysmenorrhea from severe to mild instead of severe to moderate, respondents were willing to accept, on average, a 9% additional risk of pregnancy-related problems and a 26% risk of bone fracture. These mean MARs lie outside of the risk range used in the DCE design. In addition, the MAR for bone fracture was calculated on the basis of preference weights for known levels of the risk of bone fracture that were not statistically different, suggesting that these risks were not important over the risk range used in the study. For the same improvement in treatment efficacy (improvement in dysmenorrhea from severe to mild instead of severe to moderate), respondents who had experienced moderate to severe hot flashes would accept, on average, a 16% increase in the risk of moderate to severe hot flashes, whereas

Table 4. Maximum acceptable risk calculations.

Benefit	Pregnancy	Hot flash (with experience)	Hot flash (without experience)	Bone fracture*
Levels	0%-7%	0%-85%	0%-85%	0%-10%
Dysmenorrhea				
From severe to moderate pain to severe to mild pain	9.14	15.50	37.77	25.50
From severe to moderate pain to severe to no pain	18.25	29.20	49.03	49.23
Nonmenstrual pelvic pain				
From severe to moderate pain to severe to mild pain	12.70	21.14	42.17	34.78
From severe to moderate pain to severe to no pain	18.39	30.30	49.20	49.59
Dyspareunia				
From severe to moderate pain to severe to mild pain	4.70	8.46	32.27	13.92
From no change (severe pain) to severe to mild pain	21.08	39.29	56.87	56.59
Administration				
From injection to pill or tablet	6.07	10.64	33.97	17.51

*Mean maximum acceptable risk lies outside of risk range used in the discrete choice experiment design (ie, >7% risk of pregnancy-related problems and >10% risk of bone fracture). The preference weights associated with the highest risk levels were used in a linear extrapolation to calculate this maximum acceptable risk.

respondents without that experience would accept a 38% increase in the risk of moderate to severe hot flashes.

For a change in mode of administration from injection once per month or less frequently to a pill or tablet every day, respondents were willing to accept, on average, a 6% additional risk of pregnancy-related problems and an 18% risk of bone fracture. This mean MAR lies outside of the risk range used in the DCE design. For the same change in mode of administration, respondents who have experienced moderate to severe hot flashes would accept, on average, an 11% increase in the risk of moderate to severe hot flashes, whereas respondents without that experience would accept a 34% increase in the risk of moderate to severe hot flashes.

Finally, an unknown risk of pregnancy-related problems was calculated to be equivalent to 4.66% known risk of pregnancy-related problems (95% CI 0.30 to 9.02), and an unknown risk of bone fracture was calculated to be equivalent to a 14.52% risk of bone fracture (95% CI −4.57 to 33.62). In other words, these results suggest that respondents would likely choose a treatment with a known risk of pregnancy-related problems up to 4.66% over another treatment that is identical, except that pregnancy-related risk is unknown.

Discussion

To our knowledge, this is the first published study to use a DCE to quantify preferences for attributes of treatments for endometriosis-associated pain in the United States. We found that the additional risk of moderate to severe hot flashes was the most important attribute of those included in this study. Improvements in dyspareunia, NMPP, and dysmenorrhea were the next most important attributes. Given the attributes in this study, women were not willing to trade off anything to reduce bone fracture risk over this range (0%-10%).

Our results indicate that women would be willing to accept risks to reduce endometriosis-associated pain. Specifically, improving NMPP and dyspareunia from the worst level to the next level was more important than additional improvements and more important than similar improvements in dysmenorrhea, suggesting that patients would value treatments that can improve those symptoms. Respondents' priorities for addressing the types of endometriosis-related pain should be considered in the context of their experiences with endometriosis pain treatments and may reflect that their previous therapies addressed dyspareunia and NMPP less effectively than they addressed dysmenorrhea. Moreover, respondents may have experienced greater negative impacts on their functioning and quality of life resulting from NMPP and dyspareunia compared with dysmenorrhea, which may be comparatively predictable and intermittent relative to other types of endometriosis-related pain.

The preference weights for bone fracture risk were disordered, such that higher risks were preferred to lower risks, and were not statistically significantly different from one another. These results indicate that respondents in this study did not differentiate between the levels of risk of bone fracture evaluated. As a consequence, the MARs calculated for bone fracture risk were not statistically significantly different and were outside the range of risk levels shown in the study; thus, these results are not fully interpretable. There are several possible explanations for these results. Respondents may have perceived these risks to be low and not a concern relative to the other treatment attributes in the study, may have discounted these risks because they occur "later in life," or may have believed that they could mitigate the risks of bone fracture mentioned in the survey. Although some endometriosis treatments, including the GnRH analogs, are associated with decreases in bone mineral density,[13] and bone mineral density is the best predictor of fracture risk,[28,29] no direct effect of treatment on fracture risk has been shown. Given the range of fracture risk levels used in the study (0%-10%), differences in bone fracture risks did not drive treatment choices. In addition, there were differences in MARs among women with and without experience of moderate to severe hot flashes, and those without such experience generally accepted greater risks of moderate to severe hot flashes in exchange for treatment benefits.

The available literature on patient preferences for endometriosis pain treatments is limited. A DCE study conducted in the United Kingdom evaluated patient preferences for mode of administration, ability to conceive, dysmenorrhea, pelvic pain, dyspareunia, need for pain medication, fracture risk, and cost.[30] The results of this study differed somewhat from our results, in that oral administration was the highest driver for patient preferences, whereas dysmenorrhea was the most influential pain type.

This study is subject to several limitations. The sample may not be representative of the broader endometriosis population, and patients recruited through the Endometriosis Association and SSI's web panel may have preferences that differ from those of the overall population of patients with endometriosis in the United States. In addition, diagnosis of endometriosis, along with treatment history and demographic information, was self-reported. Nearly

three-quarters of respondents had surgically diagnosed endometriosis. The proportion of respondents self-reporting a nonsurgical physician diagnosis of endometriosis (27.6%) was similar to the proportion of participants with empirically or clinically (vs surgically) diagnosed endometriosis in previous survey studies (25.8%-47.0%).[1,31] A limitation common to DCE studies is that stated preferences may differ from preferences implied by actual treatment choices, and repeated choice tasks can cause cognitive fatigue and lead to error in the results. Furthermore, our investigation evaluated preferences assuming a severe baseline level of dysmenorrhea, NMPP, and dyspareunia, which most respondents reported having experienced at any time (99.6%, 91.2%, and 78.0%, respectively). Because we did not assess improvements starting from a moderate or low level of these symptoms, the results for the few respondents who had not experienced severe dysmenorrhea, NMPP, and dyspareunia may be susceptible to hypothetical bias. Although results from online DCEs are similar to those from face-to-face interviews,[32,33] some selection bias may exist. Finally, willingness to accept risk of bone fracture among the study sample may reflect beliefs about the ability to mitigate the risk.

Conclusions

Women with endometriosis are willing to accept risks to achieve improvements in endometriosis-associated pain. Given the attributes and the levels in the study, risk of moderate to severe hot flashes was most important, and preferences varied with respondents' experience with moderate to severe hot flashes. Improvements in dyspareunia, NMPP, and dysmenorrhea were also important attributes, whereas risk of bone fracture was the least important attribute.

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Supplemental Materials

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.jval.2018.12.010.

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