GYNECOLOGY

Effect of gabapentin on sexual function in vulvodynia: a randomized, placebo-controlled trial

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BACKGROUND: Sexual dysfunction is common in women with vulvodynia.

OBJECTIVE: The purpose of this study was (1) to evaluate whether extended-release gabapentin is more effective than placebo in improving sexual function in women with provoked vulvodynia and whether there is a relationship between treatment outcome and pelvic pain muscle severity that is evaluated by palpation with standardized applied pressure and (2) to evaluate whether sexual function in women with provoked vulvodynia would approach that of control subjects who report no vulvar pain either before or after treatment.

STUDY DESIGN: As a secondary outcome in a multicenter double-blind, randomized crossover trial, sexual function that was measured by the Female Sexual Function Index was evaluated with gabapentin (1200−3000 mg/d) compared with placebo. Pain-free control subjects, matched by age and race, also completed Female Sexual Function Index for comparison.

RESULTS: From August 2012 to January 2016, 230 women were screened at 3 academic institutions, and 89 women were assigned randomly to treatment. Gabapentin was more effective than placebo in improving overall sexual function (adjusted mean difference, 1.3; 95% confidence interval, 0.4−2.2; P=.008), which included desire (mean difference, 0.2; 95% confidence interval, 0.0−3.3; P=.04), arousal (mean difference, 0.3; 95% confidence interval, 0.1−0.5; P=.004), and satisfaction (mean difference, 0.3; 95% confidence interval, 0.04−0.5; P=.02); however, sexual function remained significantly lower than in 56 matched vulvodynia pain-free control subjects. There was a moderate treatment effect among participants with baseline pelvic muscle pain severity scores above the median on the full Female Sexual Function Index scale (mean difference, 1.6; 95% confidence interval, 0.3−2.8; P=.02) and arousal (mean difference, 0.3; 95% confidence interval, 0.1−0.6; P=.01) and pain domains (mean difference, 0.4; 95% confidence interval, 0.02−0.9; P=.04).

CONCLUSION: Gabapentin improved sexual function in this group of women with provoked vulvodynia, although overall sexual function remained lower than women without the disorder. The most statistically significant increase was in the arousal domain of the Female Sexual Function Index that suggested a central mechanism of response. Women with median algometer pain scores >5 improved sexual function overall, but the improvement was more frequent than the pain domain. We hypothesize that gabapentin may be effective as a pharmacologic treatment for those women with provoked vulvodynia and increased pelvic muscle pain on examination.

Key words: gabapentin, vulvodynia, sexual function, pelvic floor

Vulvodynia, characterized by symptoms that may include stinging, burning, irritation, or itching of the vulva, is a chronic pain syndrome with a 7−16% lifetime prevalence.[1] Women with vulvodynia experience difficulties across all domains of sexual function (sexual arousal, orgasm, satisfaction, pain) as measured by the Female Sexual Function Index (FSFI),[2] a widely recognized outcome measure for sexual dysfunction. Provoked vulvodynia (PVD), the most common and best characterized subset of vulvodynia is localized to the vestibule (entry to the vagina immediately anterior to the hymenal ring) and occurs only with contact, such as from tampon insertion or intercourse. By consensus, PVD pathogenesis is multidimensional and includes dysfunction of mucosal mechanoreceptors, enhanced deeper soft tissue/muscular nociception, central sensitization, and various comorbidities. PVD-fibromyalgia comorbidity may be a classic example of a PVD subset based on a significant degree on soft tissue/muscular pain that augments vulvodynia. We previously reported that women with vulvodynia-fibromyalgia comorbidity have increased algometer pain scores and proposed that the vaginal algometer may be considered a tender point tenderness examination of the vagina.[3]

Data from the study by Arnold et al[4] suggested that gabapentin reduces the pain of fibromyalgia. If 1 of several treatable vulvodynia pain triggers is pelvic floor (levator) pain/dysfunction then treatment that reduces pelvic floor muscle pain to palpation may reduce vulvodynia pain overall. We performed a secondary analysis on women who were enrolled in a study of gabapentin and PVD arm for sexual function overall and also analyzed changes in sexual function based on levator muscles pain severity.

We hypothesized that, by reducing muscle pain, gabapentin treatment would result in improved sexual functioning. Our second hypothesis is that our affected cohort, even if they experience an increase in FSFI score, will not have scores approaching unaffected women.

Materials and Methods

Study design

This was an 18-week, multicenter, placebo-controlled, double-blinded randomized control trial with a 2-treatment,

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AJOG at a Glance

Why was this study conducted?

This study evaluated whether gabapentin is effective vs placebo in improving sexual function as measured by Female Sexual Function Index in women with provoked vulvodynia. Another purpose determined whether sexual function before or after treatment would approach that of women without provoked vulvodynia.

Key Findings

Gabapentin was more effective than placebo in improving sexual function. Women with greater muscle pain on examination responded better than those with less pain, both overall and in the arousal and pain domains. Sexual function before or after treatment was significantly lower in women with provoked vulvodynia than in those without.

What does this add to what is known?

Improvement of sexual function in women with provoked vulvodynia that is treated with gabapentin vs placebo has not been demonstrated previously. The better response of women with provoked vulvodynia with prominent muscle pain suggests that gabapentin should be considered for their treatment.

2-period crossover design that studied the efficacy of extended release gabapentin (Gralise; 1200−3000 mg/d) for localized PVD (previously known as vulvar vestibulitis).

The study was conducted between August 8, 2012, and January 19, 2016, and received institutional review board approval at the University of Tennessee Health Science Center (#10-00985-FB), Rutgers Robert Wood Johnson Medical School (#0220110309), and the University of Rochester (#31720). All participants provided written informed consent. The gabapentin (GABA) randomized controlled trial was registered in ClinicalTrials.gov (NCT1301001).

Inclusion criteria

Inclusion criteria included women who were 18−50 years old (later extended to women who were ≥50 years old because the reported upper age for vulvodynia is well >50 years of age)[5] and who reported >3 continuous months of insertional dyspareunia, pain to vulvar touch, or vulvar pain with tampon insertion or both and during pelvic examination. Participants were allowed to use oral contraceptives, hormone therapy, or selective serotonergic reuptake inhibitors if they were prescribed before randomization and were on a stable dose.

Candidates fulfilled Friedrich's criteria,[6] by their reporting tenderness of the vulvar vestibule with intercourse or touch, as with tampon insertion, with use of modified diagnostic criteria of Bergeron et al.[7] A mean score of ≥4 of 10 on a numeric rating scale of pain severity was required; however, the highest score was needed to be in the vulvar vestibule and not on the peripheral vulva area or inside the vagina.

A baseline level of pain (mean 4 of ≥10 on the 11-point tampon test [0=no pain at all; 10=worst pain ever]) was required to proceed to randomization. The tampon test has been shown to have reliability, construct validity, and responsiveness[8] and was used as the outcome measure in the primary efficacy trial.[9]

Methods and procedures

This randomized trial of 2 treatments (gabapentin and placebo) had a 2-period crossover design with 6 weeks per treatment period (4-week dose titration and 2-week maintenance dose with a 4-day washout period). Patients were assigned randomly (double-blind) in a 1:1 ratio and allocated to 1 of 2 possible treatment sequences. A trial pharmacist prepared a concealed allocation schedule by computer randomization of these 2 sequences, in blocks of 3, to a consecutive number series. Patients were assigned in turn to the next consecutive number, and the corresponding series of study drugs was dispensed. Investigators, research staff, and participants were blinded after assignment to interventions.

Participants were asked to take the oral medication in divided doses and to increase the dose incrementally regardless of point of response (pain relief). In the event of nonserious side-effects, such as sleepiness, participants were asked to decrease tablet dose each day by 1 to the lowest tolerable dose and to remain at that dose for the remainder of the clinical trial. Acetaminophen, aspirin, or nonsteroidal antiinflammatory drugs were permitted as "rescue medication" for pain and were documented, if used. The use of opioid analgesics and topical medications were protocol violations. When deemed medically necessary, an unblinding protocol was followed (which occurred in 3 women, all of whom received placebo).

Participants completed the FSFI at baseline and after 6 weeks of treatment with gabapentin and placebo (4 weeks of titration plus 2 weeks of maintenance dose). Fifty-six vulvar pain-free control subjects also completed the FSFI.

During each of the study visits, participants were evaluated by pelvic examination, cotton swab test, pelvic muscle pain severity to palpation to standardized applied pressure, and assessment of vaginal milieu; the cotton swab test was performed at the last study visit. Cotton swab test was performed on predefined points of the labia majora, minora, and lower vagina, as described.[7]

Vaginal milieu assessment included microscopic wet mount vaginal smears, Rakoff stain[10] for vaginal maturation index, Affirm (VPIII Microbial Identification System, Becton, Dickinson and Company, Sparks, MD) test to assess for vaginitis, a phenazine test tape for vaginal pH, and urine pregnancy test. Those women with vulvovaginal atrophy that was assessed by maturation index were treated with topical vaginal estrogen therapy for at least 6 weeks and rescreened for atrophy before random

assignment. Those women with vaginitis were treated and rescreened for eligibility. Vaginitis was treated, when necessary, throughout the trial.

Outcomes

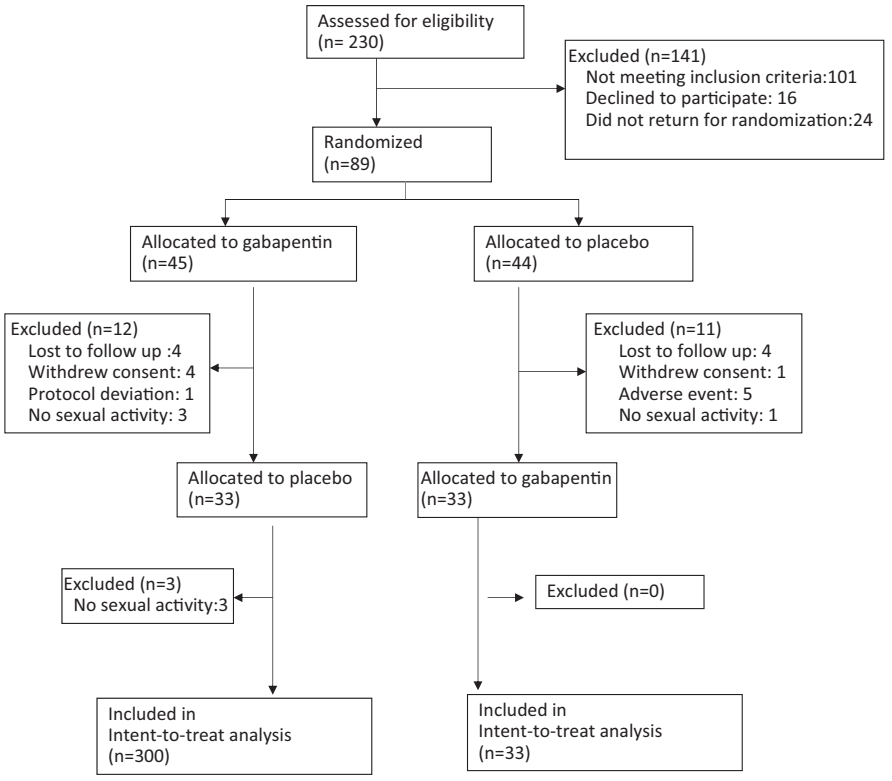
FSFI

The FSFI is a 19-item, multidimensional, self-report measure comprised of a full scale and 6 domains (desire, arousal, lubrication, orgasm, satisfaction, and pain).[2] The measure was designed for clinical trials and has demonstrated reliability, construct validity, and responsiveness. The total FSFI score (sum of the 6 domains) ranges from 2−36 points. Higher scores represent better sexual functioning, and scores below the cut-off 26.55 represent a risk of having sexual dysfunction.[11] We followed the guidelines of the authors and derived the full-scale score only in participants who had sexual activity during the measurement period. This method prevents reducing the score toward a more dysfunctional level when participants who abstain from intercourse are included. Individual domains were analyzed in all randomly assigned participants. The FSFI was administered at randomization and after 6 weeks of treatment with gabapentin and with placebo.

Pelvic muscle pain to standardized digital force

An algometer was used to assess pelvic muscle pain. This devise consists of a pressor sensor that is inserted into the vagina and allows the application of controlled force. Pelvic muscle pain severity to palpation to standardized applied pressure was performed with the use of a random staircase method and an 11-point numeric rating scale (0 [no pain] to 10 [worst possible pain]) direct scaling of pain response to a load cell-mediated, digitally applied force stimulus. Forces of 0.1, 0.3, and 0.5 kg/cm^2 were applied digitally in random assignment to the right and left iliococcygeus muscle regions. A composite algometer pain severity score was the mean numeric rating scale (0 [no pain] to 10 [worst possible pain]) for the 3 applied forces (0.1, 0.3, and 0.5 kg/cm) at the 2 iliococcygeus muscle regions.

FIGURE
Flow diagram



Seven participants were not sexually active during 1 or both treatment arms and were not included in the full-scale analysis. Data were analyzed with the use of true intention-to-treat with no missing imputations.

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Data collection

Data collection used a proprietary database platform *Slim-Prim*, (Scientific Laboratory & Patient-care Research Information management system, University of Tennessee, Knoxville, TN),[12] which is a web-accessible, modular data-based system mounted on an Oracle server that acted as the Central Data Repository. Data were entered electronically by participants remotely and by research staff at study visits. The patient responses were reviewed by the research nurse at weekly telephone calls; the accuracy of the database was validated by the data manager staff member and the principal investigator at the core site.

Sample size calculation

The number of participants randomly assigned was based on a power analysis of the primary outcome of the clinical trial, the tampon test.[9] To achieve a power of 90% and a significance level of 5% to detect a 1-point difference between the 2 phases on a scale of 0−10 of the tampon test, a sample size of 53 was needed. Assuming a dropout rate of 40%, 89 participants were assigned randomly to complete 53.

Data analysis

Demographic characteristics of trial participants were presented. Participant baseline scores on the FSFI were compared with matched vulvodynia pain-free control subjects, matched by gender, race, age (±5 years), and center with the use of a paired *t*-test.

Descriptive unadjusted means of the full FSFI and its 6 subscales were calculated for participants during the gabapentin and placebo treatment phases. The main analysis of treatment effect on FSFI scores was done with the Mixed Procedure in SAS software (version 9.4; SAS

TABLE 1
Demographic and clinical characteristics of participants

Characteristic	Participants, n (%)	
	Placebo first (n=44)	Gabapentin first (n=45)
Age, y[a]		
<52	41 (93.2)	38 (84.4)
≥52	3 (6.8)	7 (15.6)
Race		
White	14 (31.8)	16 (35.6)
Black	29 (65.9)	29 (64.4)
>1 race	1 (2.3)	0 (0.0)
Educational status		
College	29 (65.9)	27 (60.0)
No college	15 (34.1)	18 (40.0)
Duration of pain, y		
≤5	17 (38.6)	17 (37.8)
>5	27 (61.4)	28 (62.2)
History of sexual abuse		
Yes	10 (22.7)	13 (28.9)
No	34 (77.3)	32 (71.1)
Onset		
Primary	21 (47.7)	21 (46.7)
Secondary	22 (50.0)	23 (51.1)
Not reported	1 (2.3)	1 (2.2)

Data are reported according to sequence of treatment.

[a] Mean age±standard deviation: placebo first group, 35.5±11.2; gabapentin first group, 37.6±12.7.

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Institute Inc, Cary, NC) according to the crossover design and based on intent-to-treat principle. The mixed model, with participant as the random effect, combined both within individual differences and between individual differences. The model included period, treatment, and the center effect. Degrees of freedom were further adjusted with the use of the Kenward-Roger method to take account of small sample size. A subanalysis was performed to determine the effect of pelvic muscle tenderness on treatment outcome by stratification of baseline algometer scores above median (high muscle pain severity) and below median (low muscle pain severity) scores.

Model adjusted means, 95% confidence interval (CI), and mean differences were reported based on the mixed models. Statistical significance was defined as a probability value <.05 using 2-tailed tests. A completer analysis that included everyone who completed FSFI in both gabapentin and placebo groups for 6 weeks was performed on all treatment outcomes as a secondary analysis.

Results

Attrition

Figure 1 summarizes the flow diagram of progression from baseline visit to study completion. Of the 230 women who were screened, 89 women met entry criteria and were assigned randomly; 66 women completed the trial, and 63 participants had complete data on the full scale at study completion. Of the 141 participants who were excluded, 101 women did not meet inclusion criteria; 16 women decided not to participate in the trial, and 24 women did not return for drug randomization. Of the 89 individuals randomly assigned to the study drug, 8 women were lost-to-follow up; 5 women withdrew consent; 5 women were removed by research staff because of adverse events; 1 woman was removed for a protocol deviation, and 7 women were not sexually active. Data were analyzed by intention to treat with no missing imputation.

Demographic and baseline characteristics

Demographic and baseline characteristics at randomization are presented in Table 1. There were no statistically significant differences in distribution of any of the variables between the gabapentin and placebo crossover phases. The mean age of the symptomatic women was 37 years. Most of the women had attended college and had their vulvodynia pain duration of >5 years. Approximately 25% had a history of sexual abuse; approximately 25% were taking oral contraceptives; 7 women were using hormone therapy, and 2 women were using selective serotonergic reuptake inhibitors.

Approximately one-half of the participants had primary onset, and one-half of them had secondary onset of PVD. The mean age of vulvodynia pain-free control subjects was 31 years, with 48% reporting their race as black (compared with 68% of symptomatic women).

Nearly all intervention participants (88/89) were therapeutically naive to gabapentin. Comparison of the 23 individuals who did not complete the randomized phase found no difference in age, race, years of education, marital status, or duration of disease compared with participants who completed the randomized phase.

FSFI

Participants had substantially lower FSFI scores compared with vulvodynia pain-free control subjects (adjusted mean difference for full scale, 8.9; 95% CI, 7.0−10.9; $P<.0001$; Table 2). Gabapentin significantly improved scores on

TABLE 2
Baseline Female Sexual Function Index scores in participants compared with matched vulvodynia pain-free control subjects[a]

Female Sexual Function Index score[a]	Participants		Control subjects		Adjusted mean Difference (95% confidence interval)	*P* value
	N	Adjusted mean (95% confidence interval)[b]	N	Adjusted mean (95% confidence interval)		
Full[c]	56	20.7 (17.3–22.9)	53	29.0 (25.7–32.3)	8.9 (7.0–10.9)	<.0001
Desire	89	2.6 (2.2–3.1)	55	3.7 (3.1–4.3)	1.1 (0.6–1.5)	<.0001
Arousal	60	3.8 (3.2–4.4)	55	5.2 (4.5–6.0)	1.4 (0.9–1.9)	<.0001
Lubrication	60	4.1 (3.6–4.6)	54	5.5 (4.9–6.1)	1.3 (1.0–1.7)	<.0001
Orgasm	60	3.9 (3.1–4.6)	55	4.8 (3.9–5.7)	1.0 (0.4–1.5)	<.0001
Satisfaction	60	3.7 (3.1–4.3)	54	4.9 (4.1–5.6)	1.2 (0.7–1.7)	<.0001
Pain	57	2.3 (1.9–2.8)	53	5.8 (5.3–6.3)	3.5 (3.2–3.8)	<.0001

[a] Score ranges: full scale, 2 (sexual dysfunction) to 36 (no sexual dysfunction); desire, 1.2 (no desire) to 6 (very high desire); arousal, 0 (no arousal) to 6 (very high arousal); lubrication, 0 (impossible) to 6 (not difficult); orgasm, 0 (impossible) to 6 (not difficult); satisfaction, 0.8 (very dissatisfied) to 6 (very satisfied); and pain, 0 (very high) to 6 (none at all); [b] Based on general linear model, adjusted for age, race, and site; intention to treat, no missing imputation; [c] The full scale score was included for those participants who were sexually active.

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the full scale over placebo among participants (mean difference, 1.3; 95% CI, 0.4–2.2; *P*=.008; Table 3). Similarly, compared with placebo, gabapentin improved sexual desire (mean difference, 0.2; 95% CI, 0.0–3.3; *P*=.04), arousal (mean difference, 0.3; 95% CI, 0.1–0.5; *P*=.004), and satisfaction (mean difference, 0.3; 95% CI, 0.0–0.5; *P*=.02) domains but did not improve orgasm, lubrication, or pain domains. Results with completer analysis were similar to treatment outcomes with intent-to-treat analysis.

After gabapentin treatment, participant scores remained significantly lower than vulvodynia pain-free control subjects on the full scale (mean difference, 6.9; 95% CI, 4.7–9.1; *P*<.001), desire (mean difference, 0.8; 95% CI, 0.4–1.3; *P*=.0004), arousal (mean difference, 1.2; 95% CI, 0.7–1.7; *P*<.0001), satisfaction (mean difference, 1.0; 95% CI, 0.5–1.5; *P*<.0001), orgasm (mean difference, 0.8; 95% CI, 0.2–1.4; *P*=.005), lubrication (mean difference, 1.1; 95% CI, 0.7–1.5; *P*<.0001), and pain (mean difference, 2.4; 95% CI, 1.9–2.9; *P*<.0001) domains.

Pelvic muscle pain to standardized digital force

After stratification of baseline provoked pelvic muscle pain severity scores into above median (high muscle pain severity) and below median (low muscle pain severity), gabapentin improved the total FSFI of vulvodynia-afflicted subjects with high muscle pain severity (mean difference, 1.6; 95% CI, 0.3–2.8; *P*=.02) but not with low muscle pain severity (Table 4). High muscle pain severity also predicted a gabapentin effect on improved FSFI arousal score

TABLE 3
Comparison of Female Sexual Function Index scores between treatment groups

Female Sexual Function Index[a]	Placebo group		Gabapentin group, adjusted mean (95% confidence interval)	Adjusted mean difference (95% confidence interval)	*P* value
	N	Adjusted mean (95% confidence interval)[b]			
Full scale[c]	63	21.1 (18.1–24.1)	22.4 (19.4–25.4)	1.3 (0.4–2.2)	.008
Desire	89	2.7 (2.3–3.2)	2.9 (2.4–3.4)	0.2 (0.0–3.3)	.04
Arousal	68	4.2 (3.4–4.9)	4.4 (3.7–5.2)	0.3 (0.1–0.5)	.004
Lubrication	68	4.1 (3.6–4.7)	4.2 (3.7–4.8)	0.1 (−0.1–0.3)	.23
Orgasm	68	4.4 (3.7–5.1)	4.5 (3.7–5.2)	0.1 (−0.2–0.3)	.7
Satisfaction	68	4.1 (3.5–4.7)	4.4 (3.8–5.0)	0.3 (0.0–0.5)	.02
Pain	64	2.5 (1.8–3.2)	2.7 (2.0–3.4)	0.2 (−0.1–0.5)	.23

[a] Score ranges: full scale, 2 (sexual dysfunction) to 36 (no sexual dysfunction); desire, 1.2 (no desire) to 6 (very high desire); arousal, 0 (no arousal) to 6 (very high arousal); lubrication, 0 (impossible) to 6 (not difficult); orgasm, 0 (impossible) to 6 (not difficult); satisfaction, 0.8 (very dissatisfied) to 6 (very satisfied); and pain, 0 (very high) to 6 (none at all); [b] Based on mixed model, adjusted for period, treatment, and center; intention to treat, no missing imputation; [c] The full scale score was included for those participants who were sexually active.

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TABLE 4
Relationship between baseline pelvic muscle pain severity and treatment outcome

Baseline pelvic muscle pain severity[a]	Female Sexual Function Index[b]	Placebo group		Gabapentin group, adjusted mean (95% confidence interval)	Adjusted mean difference (95% confidence interval)	*P* value
		N	Adjusted mean (95% confidence interval)[c]			
≤4	Full scale[d]	28	21.0 (17.7–24.2)	22.0 (18.8–25.2)	1.0 (−0.5–2.4)	.19
	Desire	43	2.7 (2.1–3.2)	2.9 (2.4–3.4)	0.2 (−0.0–0.5)	.07
	Arousal	32	4.2 (3.4–5.0)	4.4 (3.6–5.6)	0.2 (−0.1–0.5)	.14
	Lubrication	32	4.0 (3.5–4.6)	4.2 (3.6–4.7)	0.1 (−0.1–0.4)	.28
	Orgasm	32	4.5 (3.8–5.3)	4.4 (3.6–5.1)	−0.2 (−0.5–0.2)	.35
	Satisfaction	32	4.0 (3.4–4.7)	4.3 (3.7–5.0)	0.3 (−0.1–0.7)	.10
	Pain	28	2.7 (1.9–3.4)	2.6 (1.8–3.3)	−0.1 (−0.6–0.3)	.59
≥5						
	Full	35	21.4 (17.6–25.2)	23.0 (19.1–26.8)	1.6 (0.3–2.8)	.02
	Desire	46	2.9 (2.2–3.5)	3.0 (2.4–3.2)	0.1 (−0.1–0.4)	.24
	Arousal	36	4.1 (3.2–5.1)	4.5 (3.5–5.4)	0.3 (0.1–0.6)	.01
	Lubrication	36	4.4 (3.7–5.1)	4.5 (3.8–5.2)	0.1 (−0.2–0.3)	.51
	Orgasm	36	4.2 (3.3–5.2)	4.5 (3.5–5.4)	0.2 (−0.1–0.6)	.16
	Satisfaction	36	4.2 (3.4–5.0)	4.5 (3.7–5.3)	0.3 (−0.1–0.6)	.10
	Pain	36	2.2 (1.4–3.1)	2.7 (1.8–3.6)	0.4 (0.02–0.9)	.04

[a] A composite pain severity score the mean numeric rating scale (0=no pain to 10=worst possible pain) for the selected 3 applied forces (0.1, 0.3, and 0.5 kg/cm) at the 2 iliococcygeus muscle regions; [b] Score ranges: full scale, 2 (sexual dysfunction) to 36 (no sexual dysfunction); desire, 1.2 (no desire) to 6 (very high desire); arousal, 0 (no arousal) to 6 (very high arousal); lubrication, 0 (impossible) to 6 (not difficult); orgasm, 0 (impossible) to 6 (not difficult); satisfaction, 0.8 (very dissatisfied) to 6 (very satisfied); and pain, 0 (very high) to 6 (none at all); [c] Based on mixed model, adjusted for period, treatment and center; intention to treat, no missing imputation; [d] Obtained in those participants who were sexually active and where pelvic muscle to standardized applied pressure was performed.

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(mean difference, 0.3; 95% CI, 0.1–0.6; *P*=.01) and a trend toward improved FSFI pain score (mean difference, 0.4; 95% CI, 0.02–0.9; *P*=.04), although the pain domain did not achieve statistical significance, after correction for multiple comparisons of FSFI domains.

The mean daily dose of gabapentin during maintenance was 2476±866 mg. Compliance rate, determined by retained container pill count, was 94.7%. The incidence of adverse effects was slightly higher, but not significantly different, with gabapentin compared with placebo: rhinitis (11.2% vs 4.5%), dizziness (10.1% vs 3.4%), nausea (8.9% vs 3.4%; *P*=.10), headache (7.9% vs 5.6%), somnolence (7.9% vs 4.5%), bacterial vaginosis (7.9% vs 4.5%), and fatigue (5.6% vs 1.1%). No serious adverse events occurred during gabapentin treatment.

Comment

The cause of vulvodynia is unknown and likely multifactorial, which makes diagnosis and treatment a clinical challenge. The 2015 Consensus Terminology Classification of Persistent Vulvar Pain addressed this challenge by providing definitions for vulvar pain disorders, including vulvodynia.[13] This classification recognized potential factors that are associated with vulvodynia, including musculoskeletal disorders. It recognizes the role of central sensitization that plays a role in neurologic interpretation of pain. Although impact of this classification on diagnostic and treatment algorithms remains unclear, it provides consistency in terminology for both research and clinical settings. It additionally offers clinicians a systematic approach to the vulvodynia patient and may aid in both differential diagnosis and choice of therapeutic intervention.

Evaluation of vulvodynia requires a detailed history that includes sexual and psychosocial impact of pain. Examination should exclude other vulvovaginal disorders. Palpation of the levator muscles immediately inside the vagina is necessary to assess for tenderness, which includes possible pelvic floor dysfunction. Clinically, this palpation is performed manually, and the interpretation is subjective. In our research setting, a more objective test of levator muscle tenderness was performed with the use of a vaginal algometer. This devise consists of a pressor sensor that is attached to the index finger of the examining hand and inserted into the vagina, allowing an application of controlled force.

The original study failed to show a significant improvement in overall pain with gabapentin vs control as determined by the tampon test as the primary

outcome measure. Correlation between daily tampon pain with FSFI scores showed a negative, but not statistically significant, correlation with total FSFI scores as well as all FSFI domains. This relationship persisted with combined or separated treatment and control periods.

In our secondary analysis, the impact of gabapentin on sexual function was evaluated because gabapentin has been associated with improvement in muscular conditions such as fibromyalgia. This was appropriate because, in this trial, women with pain that anatomically was located to deeper pressure specifically located over muscle groups were recruited and assigned randomly. This secondary analysis showed an improvement in sexual function in women with higher baseline muscle pain severity score, which suggests that the effect of gabapentin may be on reducing muscle pain. This is consistent with the conclusion of the primary analysis in that there was no correlation with decreased pain with gabapentin when measured as a function of the tampon test, which measures a more superficial peripheral nerve response. This secondary outcome suggests that gabapentin treatment might be more beneficial in women with PVD whose pain is triggered by pressure on the pelvic floor. Overall, these data suggested that gabapentin was more effective than placebo in improving overall sexual function as measured by the FSFI, with overall scores increased by 1 between gabapentin and placebo (P=.008). Our overall pretreatment score range was 17.3−22.9. Data from several studies that used FSFI as an outcome measure for vulvodynia interventions reported an average upper range of pretreatment FSFI score at 17, with posttreatment scores up to 22.68, which shows not only a numerically greater impact of treatment but also with lower scores than our normal control subjects.[14−16]

Further, the statistically significant increase in FSFI score suggests a beneficial gabapentin effect on sexual function over placebo. The individual domains of desire, arousal, and satisfaction were statistically significantly increased, with the most significant improvement in the domain of arousal (P=.004). Because the most significant improvement was seen in the arousal domain, a primarily central response is suggested vs lubrication, which measures peripheral function and was not statistically significantly improved.

The individual domain of pain was not statistically improved, which suggests that sexual function may not be correlated directly with overall pain or tenderness because of the intervention's peripheral effect on muscle, but severity of the muscle dysfunction. That is, when looking at these data in accordance with our hypothesis that gabapentin would improve sexual functioning secondary to a beneficial effect on muscle pain, we found that gabapentin intervention had a better overall response in women with a higher median baseline algometer pain score ($\geq$5/10). These women showed a significant change in overall FSFI measured sexual function and the domains of arousal and, as opposed to the entire cohort, pain, which suggests that, in this cohort of women with increased muscle pain at baseline, both a central mechanism of action (arousal) and a peripheral mechanism of action (pain) may lead to better sexual function.

The second component of the study, which matched our cohort by age and race with women who did not report vulvar pain, suggested that not only did women with PVD have significantly lower FSFI overall sexual function but also, even after treatment the improvement in the PVD cohort, the improvement did not approach the level of sexual functioning in women without the disorder.

Our data, although statistically significant, showed minimal numeric improvement between gabapentin and placebo as measured by the FSFI. The increase in placebo response may have been affected by the instructional examinations and clinical counseling that were given to participants. These nonpharmacologic interventions may have contributed to a more positive attitude towards sexual function. The clinical significance of the FSFI change is difficult to assess.

Our findings add to the literature in the clinical management of vulvodynia by demonstrating a small, but significant, improvement of sexual function in women who are treated with gabapentin over placebo. The key clinical relevance, however, may be the better response of women with higher median algometer pain scores, which clinically may translate to considering gabapentin as an initial treatment option in women with PVD who report more severe muscle pain on pelvic floor examination.

The strengths of our study include a demographically and geographically diverse population, the use of validated questionnaires, and the use of a standardized muscle pain score (algometer). Our study limitations include a treatment duration of only 6 weeks and a lack of a no-treatment arm to determine true placebo effect. Finally, although our control group was well matched and screened, only a small portion (n=10) underwent physical examination and cotton swab testing.

Gabapentin improved sexual function in this group of women with PVD, although overall sexual function remained lower than women without the disorder. The highly significant increase in the arousal domain of the FSFI suggests a central mechanism of response. Those women with median algometer pain scores of $\geq$5 of 10 had a greater response overall, and their improvement of the pain and the arousal domains suggests both a central and peripheral action in this cohort. Gabapentin should be considered for treatment in women with PVD who have increased pelvic muscle pain as noted on examination. ■

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References

1. Harlow BL, Stewart EG. A population-based assessment of chronic unexplained vulvar pain: have we underestimated the prevalence of vulvodynia? J Am Med Women's Assoc 2003;58:82–8.

2. Rosen R, Brown C, Heiman J, et al. The Female Sexual Function Index (FSFI): a multidimensional self-report instrument for the assessment of female sexual function. J Sex Mar Ther 2000;26:191–208.

3. Phillips NA, Brown C, Bachmann G, et al. Relationship between nongenital tender point tenderness and intravaginal muscle pain intensity: ratings in women with provoked vestibulodynia and implications for treatment. Am J Obstet Gynecol 2016;215:751–3.

4. Arnold LM, Goldenberg DL, Stanford SB, et al. Gabapentin in the treatment of fibromyalgia: a randomized, double-blind, placebo-controlled, multicenter trial. Arthritis Rheum 2007;56:1336–44.

5. Reed BD, Harlow SD, Sen A, et al. Prevalence and demographic characteristics of vulvodynia in a population-based sample. Am J Obstet Gynecol 2012;206:170.e1–9.

6. Friedrich EG. Vulvar vestibulitis syndrome. J Reprod Med 1987;32:110–4.

7. Bergeron S, Binik YM, Khalife S, Pagidas K, Glazer HI. Vulvar vestibulitis syndrome: reliability of diagnosis and evaluation of current diagnostic criteria. Obstet Gynecol 2001;98:45–51.

8. Foster DC, Kotok MB, Huang LS, et al. Oral desipramine and topical lidocaine for vulvodynia: a randomized controlled trial. Obstet Gynecol 2010;116:583–93.

9. Brown C, Bachmann GA, Wan J, Foster DC; for the Gabapentin (GABA) Study Group. Gabapentin for the treatment of vulvodynia: a randomized controlled trial. Obstet Gynecol 2018;131:1000–7.

10. Rakoff AE. The endocrine factors in pelvic tumors, with a discussion of the Papanicolaou smear method of diagnosis. Radiology 1948;50:190–201.

11. Wiegel M, Meston C, Rosen R. The Female Sexual Function Index (FSFI): cross-validation and development of clinical cutoff scores. J Sex Mar Ther 2005;31:1–20.

12. Viangteeravat T, Brooks IM, Smith EJ, et al. Slim-prim: a biomedical informatics database to promote translational research. Perspect Health Inf Manag 2009;6:6.

13. Bornstein J, Goldstein AT, Stockdale CK, et al. 2015 ISSVD, ISSWSH and IPPS consensus terminology and classification of persistent vulvar pain and vulvodynia. Obstet Gynecol 2016;127:745–51.

14. Pelletier F, Girardin M, Humbert P, Puyraveau M, Aubin F, Parratte B. Long-term assessment of effectiveness and quality of life of OnabotulinumtoxinA injections in provoked vestibulodynia. J Eur Acad Dermatol Venereol 2016;30:106–11.

15. Schlaeger JM, Xu N, Mejta CL, Park CG, Wilkie DJ. Acupuncture for the treatment of vulvodynia: a randomized wait-list controlled pilot study. J Sex Med 2015;12:1019–27.

16. McDonald JS, Rapkin AJ. Multilevel local anesthetic nerve blockade for the treatment of generalized vulvodynia: a pilot study. J Sex Med 2012;9:2919–26.

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