Topical Gabapentin in the Treatment of Localized and Generalized Vulvodynia

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OBJECTIVE: To evaluate the clinical efficacy and tolerability of topical gabapentin in the treatment of women with vulvodynia.

METHODS: A retrospective study was designed to ascertain clinical responses to topical gabapentin. Patient demographic and medical characteristics, including present and prior treatment for vulvodynia, were routinely collected. The final outcome was defined by a comparison between pretreatment and posttreatment mean pain scores based on a discrete visual analog scale of 0 to 10. Categorical data were compared by Fisher exact test, continuous variables between groups by the Wilcoxon rank sum test, and mean change in pain score between pretreatment and posttreatment by paired Student *t* test.

RESULTS: Between January 2001 and December 2006, 51 women with vulvodynia (19 or 37% with generalized vulvodynia, 32 or 63% with localized) were treated with 2% to 6% gabapentin. After a minimum of 8 weeks of therapy, the mean pain score among the 35 evaluable women was significantly reduced from 7.26 to 2.49 (mean change −4.77, 95% confidence interval −5.47 to −4.07). Overall, 28 of 35 (80%) demonstrated at least a 50% improvement in pain scores. Among patients with localized vulvodynia, sexual function improved in 17 of 20 with evaluable results (6 of 9 reinstituted vaginal intercourse, whereas all 11 patients experiencing decreased frequency of intercourse reported increased frequency after treatment). Discontinuations occurred in 7 of 50 (14%) treated.

CONCLUSION: Topical gabapentin seems to be well-tolerated and associated with significant pain relief in women with vulvodynia.

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LEVEL OF EVIDENCE: III

In 2002 and again in 2006, the National Institutes of Health characterized vulvodynia (defined as chronic, unexplained vulvar pain or discomfort, characterized by burning, stinging, irritation, or rawness) as a poorly understood and underresearched focal pain syndrome for which optimal treatment remained unclear. Current evidence indicates that the lifetime cumulative incidence of vulvodynia approaches 15%, which suggests that nearly 14 million U.S. women may at some point in their lives experience the symptoms of chronic vulvar burning and pain.[1] Indeed, a localized form of vulvodynia involving the vulvar vestibule is thought to be the leading cause of dyspareunia in premenopausal women.[2,3]

Patients with vulvodynia tend to fall into different groups based on the location of their pain. Generalized vulvodynia is used to describe involvement of the entire vulva by persistent, chronic pain that is burning, stinging, or irritating in nature, whereas localized vulvodynia specifies involvement of only a portion of the vulva, such as the vestibule or the clitoris. In both generalized and localized vulvodynia, the pain may be provoked (ie, triggered by physical contact of a sexual and/or nonsexual nature), unprovoked, or both. In the case of provoked pain, common triggers include, for example, intromission (resulting in introital dyspareunia) or tampon insertion.[4] Treatment recommendations are similar for both localized and generalized vulvodynia and range from

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topical therapies to oral medications, physical therapy and biofeedback, and surgical excision, although the latter is reserved for women with localized pain only. Although many of these modalities demonstrate efficacy, many are associated with adverse effects, require numerous visits to physicians, or are invasive.

The purpose of this study is to assess retrospectively clinical responses (reduction in pain and changes in sexual function) and product tolerability associated with the use of topical gabapentin, a novel form of therapy, among women with vulvodynia. Data on oral gabapentin in the successful management of neuropathic pain syndromes (including vulvodynia), combined with evidence suggesting a peripheral process in the development of vulvodynia, led to our hypothesis that gabapentin cream, if efficacious and well-tolerated, could be a useful addition to the treatment options currently available to women with chronic vulvar pain syndromes.

MATERIALS AND METHODS

Using a database established by the study authors, we identified all women presenting to the Women and Infants' Vulvar Clinic between January 1, 2001, and December 30, 2006, with the diagnosis of localized or generalized vulvodynia. The International Society for the Study of Vulvovaginal Disease defines vulvodynia as vulvar discomfort, most commonly described as burning pain, occurring in the absence of relevant visible findings (such as infection or inflammation) or a specific, clinically identifiable neurologic disorder (for example, herpetic neuralgia).[4–7] To receive the diagnosis of vulvodynia, we required that women report chronic (present for 3 or more months) vulvar pain of unknown cause. Patients were further characterized as having localized vulvodynia if they described severe pain on touch or attempted vaginal entry, and on examination using the cotton-swab test, had tenderness to pressure localized to the vulvar vestibule of at least 4 of 10. In all patients, other causes of vulvar burning or pain were ruled out with cervicovaginal culture and if indicated by examination biopsy.

To be eligible for inclusion in the present study, patients had to have fulfilled the criteria above for either generalized or localized vulvodynia and been prescribed treatment with topical gabapentin. Prior or concomitant use of other therapies, including oral gabapentin, was not precluded. Pregnant or lactating women or women actively seeking to become pregnant were not prescribed topical gabapentin. It is of note that in our practice, patients diagnosed with vulvodynia are offered treatment, unless contraindicated, with a variety of local and oral medications, as well as biofeedback and physical therapy. The final choice of treatment is made after a discussion between the patient and the provider.

In brief, two local compounding pharmacists prepared the gabapentin cream by dissolving gabapentin powder in ethoxy diglycol, then levigating the mixture into PCCA Lipoderm base (PCCA, Houston, TX), an enhanced base which facilitates tissue penetration, and placing the final product in plastic tubes for dispensation. Creams were dispensed as 2%, 4%, or 6%; the initial choice of dose was determined by the provider. In general, postmenopausal women were initially started on one of the two lower doses secondary to concerns over irritation; if, however, the therapeutic effect was suboptimal and the product tolerated, a higher dose was then prescribed. Initial product testing on the 6% gabapentin cream revealed the finished product was 93% of stated dose, and product stability estimates at 30, 60 and 90 days postpackaging remained in excess of 90% of the expected dose (Analytical Research Laboratories, Oklahoma City, OK). Patients were instructed to apply a small amount of cream (approximately 0.5 mL, equivalent to the size of a pea) three times daily.

For the current study, demographic information, including age, race/ethnicity, marital status, gravidity/parity, insurance status, as well as information on prior and current use of birth control, history of vaginal infections and history of abuse were gathered using the database, augmented by chart review as necessary. Data on the duration of vulvar pain and prior use of any medications, over-the-counter products, physical therapy or biofeedback, alternative therapies, or surgery was also collected. The primary study outcome was defined as the difference in the individual patient's pretreatment and posttreatment pain scores as measured on a discrete visual analog scale of 0 (no pain) to 10 (worst possible pain). Patients with localized vulvodynia were also evaluated using the Marinoff dyspareunia scale (Level I or causes discomfort but does not prevent sexual intercourse; Level II or frequently prevents sexual intercourse; Level III or completely prevents sexual intercourse) before and following treatment.

All statistical analyses were done using Stata 9 (StataCorp, College Station, TX). Categorical variables were compared by Fisher exact test, whereas continuous variables were compared between groups by the Wilcoxon rank sum test. The posttreatment visit pain score was subtracted from the pretreatment visit score to determine a change in pain score for each subject and a mean change in score for each group. The change in pain score from pretreatment to posttreatment was

compared using paired *t* tests, whereas the change in pain score was compared between groups by the Wilcoxon rank sum test. Approval for this retrospective project was obtained from the Women and Infants' Institutional Review Board before project initiation.

RESULTS

Between January 2001 and December 2006, 51 of 210 (24%) women diagnosed with generalized or localized vulvodynia were seen in the Vulvar Clinic at Women and Infants Hospital and treated with 2% to 6% topical gabapentin, either alone or in combination with other therapies. Patients reported symptoms consistent with either generalized (19 or 37%) or localized (32 or 63%) vulvodynia for a mean duration of 75.4 months (range 3–480 months). The median age of women treated with topical gabapentin was 34, with a mean age (±standard deviation) of 40.2 years (±16.3 years). The majority were white (48 or 94%), married (27 or 53%), and privately insured (50 or 94%). Women with localized vulvodynia were significantly more likely to be younger (median age 31 years compared with 51 years for women with generalized vulvodynia, $P<.001$), unmarried (47% compared with 11%, $P=.01$) and of lower parity (0 compared with 2, $P=.001$). Hormonal contraception was reported in 14 or 44% of women with localized vulvodynia, whereas 7 of 19 (37%) of the women with generalized vulvodynia had undergone prior hysterectomy (Table 1 for full details). The most frequently reported prior vaginal infection was candidiasis (22 or 43%), with complicated candidiasis (defined as recurrent and/or atypical) occurring in 12 or 24%.

The mean duration of vulvar pain in the population was 75.4 months (median 30 months, range 3–480 months). The majority of women had received

Table 1. Population Characteristics, as a Group and by Localized Compared With Generalized Vulvodynia

	Localized Vulvodynia (n=32)	Generalized Vulvodynia (n=19)	*P*
Age (y)	32.9 (±10.6)/31	52.4 (±17.1)/51	<.001*
Marital Status			
Single	15 (47)	2 (11)	.01
Married	15 (47)	12 (63)	
Divorced	1 (3)	4 (21)	
Widowed	1 (3)	1 (5)	
Race/ethnicity	30 (94)	18 (95)	1.0
White	2 (6)	1 (5)	
Hispanic			
Gravidity	0.81 (±1.14)/0	2.18 (±1.47)/3	.001*
Parity	0.52 (±0.81)/0	1.65 (±1.22)/2	.001*
Insurance			
Private	31 (97)	19 (100)	1.0
Medicaid/self	1 (3)	0	
History of abuse			
Physical	1 (3)	0	.2
Sexual	1 (3)	0	
Both	6 (19)	8 (42)	
Birth control			
Hormonal (oral contraceptives, patch or ring)	14 (44)	2 (11)	.02
Condoms	5 (16)	0	.1
Intrauterine device	1 (3)	0	1.0
Tubal or vasectomy	1 (3)	3 (16)	.1
Postmenopausal	3 (9)	5 (26)	.1
Hysterectomy	2 (6)	7 (37)	.009
None or not active	5 (15)	2 (11)	.7
Prior vaginal infections			
Candidiasis	13 (41)	9 (47)	.8
Bacterial vaginosis	3 (9)	3 (16)	.7
Herpes simplex	1 (3)	4 (21)	.06
Trichomonas, gonorrhea and/or chlamydia	3 (9)	0	.3
Atrophic vaginitis	2 (6)	5 (26)	.09
Desquamative inflammatory vaginitis	0	1 (5)	.4
None	16 (50)	6 (32)	.3

Data are mean (±standard deviation)/median or n (%).
* Difference between diagnoses by the Wilcoxon rank sum test.

one or more prior therapies, including most commonly topical lidocaine (19 or 37%), antifungal preparations (17 or 33%), hormonal medications (16 or 31%), tricyclic antidepressants (13 or 25%), and anticonvulsants (8 or 16%). Women with generalized vulvodynia were significantly more likely to have used both hormonal therapies and anticonvulsants. At the time topical gabapentin therapy was begun, 19 or 40% were using other medications, most often tricyclics in the generalized vulvodynia population (3 of 9) and topical lidocaine in women with localized vulvodynia (6 of 10) (Table 2).

Of the 51 women prescribed topical gabapentin, 16 of 32 (55%) with localized vulvodynia and 6 of 19 (32%) with generalized vulvodynia received the highest dose of cream (6% gabapentin), whereas 9 of 32 (31%) and 9 of 19 (47%), respectively, received the lowest dose, 2% gabapentin (P=.25); it is of note that the remaining 7 of 32 (22%) of women with localized vulvodynia and 3 of 19 (16%) with generalized vulvodynia were treated with 4% gabapentin).

Table 2. Vulvar Symptom Duration, Medications Used

	Localized Vulvodynia (n=32)	Generalized Vulvodynia (n=19)	*P*
Pain duration (mo)			
Mean±standard deviation	74.8±103.0	76.3±103.6	.7*
Median (range)	36 (3–480)	24 (4–300)	
Prior therapy	6 (19)	7 (37)	.2
Tricyclic antidepressants	2 (6)	6 (32)	.04
Anticonvulsants	14 (44)	5 (26)	.2
Lidocaine	2 (6)	3 (16)	.3
Antibiotics	7 (22)	9 (47)	.07
Hormonal	3 (9)	0	.3
Lubricants	11 (34)	6 (32)	1.0
Antifungals	3 (9)	5 (26)	.1
Steroids	1 (3)	0	1.0
Low oxalate diet	1 (3)	2 (11)	.5
Biofeedback	2 (6)	0	.5
Surgery	1 (3)	1 (5)	1.0
Anti-HSV	3 (9)	0	.3
SSRIs	3 (9)	0	.3
None			
Using other therapy when topical gabapentin begun	10 (33)	9 (53)	.2
Tricyclic antidepressants	1 (10)	3 (33)	.3
Anticonvulsants	0	1 (11)	.5
Lidocaine	6 (60)	1 (11)	.06
Hormonal	0	2 (22)	.2
Antifungals	2 (20)		.09
Steroids	0	3 (33)	.5
Biofeedback	2 (20)	0	

HSV, herpes simplex virus; SSRI, selective serotonin reuptake inhibitor.
Data are n (%) except where otherwise specified.
* Difference between diagnoses by the Wilcoxon rank sum test.

Of the 35 patients with evaluable pretherapy and posttherapy responses, 28 (80%) demonstrated at least a 50% improvement in pain scores after treatment, with 10 (29%) reporting complete pain relief after at least 8 weeks of topical gabapentin use (Table 3). Before beginning therapy, the mean (±standard deviation) pain score was 7.26 (±2.16). After a minimum of 8 weeks of therapy, the mean pain score was significantly reduced to 2.49 (mean change −4.77, 95% confidence interval [CI] −5.47 to −4.07). Among women with localized vulvodynia, the mean pretreatment score of 7.92 (±2.04) was significantly reduced to 2.71 (±1.63) after therapy (mean change −5.21, 95% CI −5.59 to −4.42). Similar changes were seen in women with generalized pain (pretreatment score 5.82 [±1.72], posttreatment 2.00 [±2.32]; mean change −3.82, 95% CI −5.25 to −2.38). In the patients reporting localized vulvodynia, 17 of the 20 with evaluable results reported an improvement in sexual function (6 of the 9 unable to have vaginal intercourse before treatment were able to do so after therapy, whereas all 11 reporting decreased frequency of vaginal intercourse before therapy noted increased frequency after treatment). Last, in separate analyses assessing first the effect of the dose of topical gabapentin and second, the concomitant use of other medications, no significant differences arose in changes in mean pain scores or changes in sexual function among the localized vulvodynia patients. Such analyses, however, were restricted as a result of small sample size, and conclusions cannot be drawn.

Discontinuations occurred in 7 of the 50 (14%) treated, three for local irritation and four for urinary complaints (including transient retention, frequency, and repetitive urinary tract infections). Upon discontinuation, the adverse effects noted above resolved. Common adverse effects of oral gabapentin, including dizziness, somnolence, and peripheral edema, were not reported by any of the 50 patients studied.

DISCUSSION

Although a multifactorial process is most likely involved in the development of vulvodynia, the end result seems to be neuropathically mediated pain manifested predominantly as burning. In general, neuropathic pain is believed to result from damage to and loss of peripheral afferent elements, a loss that leads ultimately to changes in the central nervous system. Although inflammatory infiltrates in vestibular tissue have been seen inconsistently in women

Table 3. Change in Pain Score Overall and by Diagnosis, Among Patients With Evaluable Scores

	Localized Vulvodynia (n=24)	Generalized Vulvodynia (n=11)	*P*
Pretreatment pain score	7.92±2.04/8 (3–10)	5.82±1.72/5 (4–9)	
Posttreatment pain score	2.71±1.63/2.5 (0–6)	2.00±2.32/1 (0–7)	
Change in pain score	–5.21±1.86/–5 (–2 to –8)	–3.82±2.14/–4 (0 to –8)	
95% CI for mean	–5.99 to –4.42	–5.25 to –2.38	.07*
P value for mean†	<.001	<.001	
Complete pain relief posttreatment	4 (17)	6 (55)	
95% CI for %	6–37%	28–79%	.04

CI, confidence interval.
Data are mean±standard deviation/median (range) or n (%) except where otherwise specified.
* Difference in change in pain score between diagnoses by Wilcoxon rank sum test.
† Difference in mean score between pretreatment and posttreatment by paired *t* test.

both with and without localized vulvodynia,[8,9] evidence in favor of a predominant peripheral process has continued to accumulate. Evidence of elevated concentrations of proinflammatory cytokines[10] and vestibular nerve fiber proliferation[11] in women with localized vulvodynia provide a morphologic basis for enhanced neuronal firing when pressure is applied to the vestibule. Further supporting this hypothesis of a peripheral process in localized vulvodynia is the observation of the efficacy of surgical skin removal by vestibulectomy,[12] but not perineoplasty (undercutting of the area without excision of skin and nerve fibers) in relieving pain.[13]

Treatment recommendations, although numerous, have rarely been based on evidence from randomized trials. For instance, although tricyclic antidepressants and anticonvulsants are mainstays of therapy for women with both generalized and localized vulvodynia,[14] published data confirming their efficacy in these populations remain limited.[15–17] Moreover, the adverse effects associated with these medications, particularly the anticholinergic effects seen with the tricyclics and the sedation and dizziness of the commonly prescribed anticonvulsant gabapentin, can limit their clinical applicability. For example, in a placebo-controlled trial of amitriptyline in the treatment of patients with interstitial cystitis, 92% of the tricyclic antidepressant users, none of whom used a dose greater than 100 mg, experienced adverse effects, most commonly mouth dryness.[18]

Topical therapy should largely circumvent such adverse effects for at least two reasons. First, the amount of active drug in topical preparations is significantly less than that administered orally, and second, the topical route of delivery reduces systemic absorption of the medication. Transdermal 6% gabapentin (60 mg/mL) applied as described will result in a total daily exposure of approximately 100 mg of active drug, well below the therapeutic ranges necessary with oral administration and equivalent to the recommended maximal dosages for patients with marked renal impairment. By changing the route of administration, the occurrence of such adverse effects seems to decrease. For instance, in a trial of two medications that currently exist in commercially available topical forms, 5% doxepin (another tricyclic antidepressant) and 0.025% capsaicin, overall pain scores among patients with nongynecologic neuropathic pain were significantly reduced, whereas drowsiness occurred among only 15% of patients exposed to topical doxepin[19] as opposed to the 92% reported in van Ophoven et al's[18] trial. Although the one published randomized placebo-controlled trial of topical therapy (cromolyn sulfate) for the treatment of vulvodynia failed to show benefit,[20] investigators have demonstrated favorable clinical responses using a variety of local therapies in a number of case series and small, uncontrolled trials in this population. Topical nitroglycerin,[21] topical lidocaine,[22] and topical capsaicin[23] have all demonstrated promise as treatments for localized vulvodynia. Adverse effects, including headaches with topical nitroglycerin and local irritation with topical capsaicin, however, have limited the use of these medications.

A treatment that will be effective, easy to use, well-tolerated and associated with high compliance is clearly needed for women with vulvodynia, a condition for which patients frequently see multiple providers before arriving at the diagnosis. Based on our findings, topical gabapentin has the capacity to fulfill these criteria. As background, gabapentin was first approved by the U.S. Food and Drug Administration in 1993 for the adjunctive treatment of epilepsy and in 2002 for the treatment of postherpetic neuralgia. Although the precise mechanism of action is unknown, the inhibition of the synthesis of the excitatory neurotransmitter glutamate and the potentiation of inhibitory GABAergic transmission is most likely

relevant. Used orally, gabapentin has been shown to be effective in the management of a variety of focal neuropathic pain syndromes, including not only postherpetic neuralgia, but also painful diabetic neuropathy, glossodynia and vulvodynia.[16] For example, in one case series of 17 patients with vulvodynia, 14 (82%) responded to therapy with up to 1,200 mg of gabapentin daily.[24]

At present, however, data on local or topical use of gabapentin has been limited to animal studies. In two studies, injectable gabapentin demonstrated analgesic effects on peripheral nociception in rats.[25,26] These antihyperalgesic properties were further shown not to be due to a systemic effect. Although the precise mechanism by which gabapentin exerts its analgesic properties remains unclear, these results indicate that gabapentin has a peripheral site of action. As such, gabapentin has been postulated to offer a novel therapeutic option for topical or local treatment of pain of peripheral origin.[27] Last, although the safety of oral gabapentin is well documented,[28] topical application seemed to largely circumvent the more common systemic adverse effects of oral therapy, such as sedation, fatigue, dizziness, and confusion. Local adverse effects did lead to a discontinuation rate of 14% in our study population. This discontinuation rate, however, was lower than that observed in a pilot study of topical nitroglycerin, where 18% of women discontinued the medication because of headaches, and among those who adhered, 67% continued to experience mild to severe headaches.[21]

Unlike any single modality currently used to treat vulvodynia, topical gabapentin, as demonstrated in the present study, has the potential to simultaneously alleviate the pain associated with this disorder (and improve sexual function in those with localized vulvodynia), while maintaining high patient acceptability and tolerability. Because of the route of administration, adverse effects were minimized, and compliance was high, because the treatment was self-applied and did not require repeated provider visits. Although our results with the use of topical gabapentin in women with vulvodynia have been encouraging, we realize the limitations of such retrospective assessments of efficacy. The complexity of vulvar pain syndromes and the unclear rate of resolution in the absence of therapy coupled with our inability to control for all the potential variables that might affect the measurement of pain outcomes require a randomized clinical trial. A clinical trial that is sufficiently large, randomized, and carefully designed, implemented, and analyzed can provide the strongest and most direct evidence on which to make a judgment about the existence of a cause and effect relationship.

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