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# Open-label Trial of Lamotrigine Focusing on Efficacy in Vulvodynia

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## Abstract

**OBJECTIVE—**Chronic pelvic pain (CPP) affects 15% of women and has a high rate of psychiatric comorbidity. Vulvodynia, a vulvar pain syndrome that includes vulvar vestibulitis, is the most common subtype of CPP. This study examined the efficacy of lamotrigine for the treatment of CPP using an open-label design.

**STUDY-DESIGN—**Forty-three women with CPP were recruited from a specialty pelvic pain clinic. Of these, 31 completed 8 weeks of active treatment. Outcome variables included the McGill Pain Rating Index and subscales of pain intensity and the Hamilton Depression and Anxiety Rating Scales.

**RESULTS—**We found significant reductions in all pain and mood measures at the 8-week visit compared to baseline. In particular, women with vulvodynia-type CPP (N=17) had robust reductions in pain and mood symptoms.

**CONCLUSION—**CPP is a heterogeneous disorder, with psychiatric comorbidity and poor treatment response. This open-label study suggests that treatment with lamotrigine in women with the vulvodynia subtype of CPP may be helpful in addressing both the pain and mood symptoms associated with this disorder.

### Keywords

depression; lamotrigine; pelvic pain; vulvodynia; vulvovaginal pain

We found a clinically significant response to treatment with lamotrigine as evidenced by decreased pain scores … and improved mood and anxiety symptoms.

Chronic pelvic pain (CPP) has been estimated to affect 15% of the adult female population and account for 1 in 7 primary health care visits and 40% of diagnostic laparoscopies performed in general hospitals.[1,2] CPP has been defined as noncyclic pelvic pain of >6 months duration that is not relieved by opioid medications.[1] CPP is a heterogeneous disorder with multiple and often unknown causes and poor treatment response.[3,4] Symptoms of CPP

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can include dysmenorrhea, dyspareunia and other nonspecific complaints of lower abdominal and vulvar pain.[5–7] Previous studies have demonstrated high rates of psychiatric disorders in patients with various types of chronic pain,[8] and CPP, in particular, has been associated with a high prevalence of depression and posttraumatic stress disorder (PTSD).[9]

Although multiple studies have shown an association between abuse and psychologic distress with pelvic pain, it remains unclear whether all types of CPP disorder are equally affected. Two studies demonstrate that women with vulvodynia (pain localized to the vulva) are less likely to have psychologic disturbance, sexual and/or physical abuse history, severe pain and other somatic complaints compared with women with other types of CPP.[10,11] Alternatively, women with diffuse pain conditions report more depression, anxiety and severity of pain than women with more focused pain,[12] and those with intermittent pain (cyclical, i.e., with dysmenorrhea) have less psychologic distress and fewer histories of abuse than those with continuous chronic pain.[13] Leserman et al[14] recently formulated 7 diagnostic subtypes of CPP and noted that patients with diffuse abdominal or pelvic pain had more trauma and worse mental and physical health status compared with patients with vulvovaginal pain and cyclic pain.

The vulvar pain syndromes vulvodynia and vulvar vestibulitis, which have recently been reclassified by the International Society for the Study of Vulvovaginal Disease under the common diagnosis of vulvodynia, are the most common type of CPP.[15] Although the cause of vulvodynia remains unclear, current theories state that it may be a disorder of the central nervous system (CNS) pain regulatory pathways.[15,16] Multiple treatment options are available for vulvodynia with varying degrees of efficacy, but one of the most common is tricyclic antidepressants (TCAs).[15,1] TCAs, however, have significant side effects and demonstrate inconsistent efficacy in pelvic pain.[18] Therefore, because many women with CPP are often refractory to treatment and have significant psychiatric comorbidity, we were interested in studying the efficacy of a CNS agent, lamotrigine, which is an anticonvulsant with demonstrated efficacy in both mood and pain symptoms.

Lamotrigine (Lamictal, GlaxoSmithKline Pharmaceuticals, Durham, North Carolina), 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine, is an anticonvulsant and mood-stabilizing medication that acts by stabilizing the slow inactivated conformation of type IIA neuronal sodium channels, resulting in inhibition of repetitive firing of action potentials under conditions of sustained neuronal depolarization.[19] Lamotrigine is thought to suppress the excessive release of excitatory amino adds (principally glutamate). Glutamate, a candidate neurotransmitter in spinal cord nociceptive pathways, has been implicated in the mechanisms that may be involved in chronic pain, such as central sensitization and wind-up, both of which can be inhibited by NMDA (*N*-methyl-D-aspartic acid) receptor antagonists.[20] By inhibiting the pathologic release of glutamate, lamotrigine has the potential to be antinociceptive and prevent the mechanisms responsible for the establishment of chronic pain. Lamotrigine has FDA approval for treatment of bipolar major depression and more recently lamotrigine has also been demonstrated to be useful for the treatment of chronic pain syndromes. It has been shown to be efficacious in treating neuropathic pain in patients with diabetes and human immune deficiency (HTV) infection, including recent randomized controlled trials (Level I),[21–25] and migraine pain.[26] However, to date no studies have

examined the efficacy of lamotrigine for CPP, a pain condition that continues to be a major therapeutic challenge.

In this study, we performed an open-label trial to determine how lamotrigine would affect degree of pelvic pain, number of somatic complaints, psychologic distress (depression and anxiety) and quality of life in women with CPP, with a particular focus on vulvodynia-type pain. We also included patients with other subtypes of pelvic pain, including generalized diffuse abdominal pain and neuropathic pain.

## Materials and Methods

### Sample

In this open-label trial of lamotrigine, we screened and enrolled 43 women with CPP, with a particular focus on vulvodynia, from the University of North Carolina Pelvic Pain Clinic from November 2004 to December 2006. Of these, 31 (72%) completed the full 8 weeks of the active treatment phase and were considered study completers. Twelve women dropped out before week 8, and 9 of these 12 dropped out very early in the study as a result of concerns unrelated to the study medication; 7 decided not to participate in the study because of inconvenience (e.g., travel distance, frequency of study visits or concerns about participating in research), and 2 developed unrelated and unexpected health problems. The remaining 3 of 12 subjects developed medication side effects (minor rash, headache and fatigue) that resulted in leaving the study. The 31 completers did not differ from the 12 who dropped out on education or because of type of CPP diagnosis, however, those who dropped out tended to be on average 8 years younger ($p=0.05$). Of the 31 completers, 10 discontinued the study during the maintenance phase of treatment (between weeks 8 and 12). Most of those who dropped out in the maintenance period experienced medication side effects, including fatigue, nausea, headaches and rash. Thus 21 patients completed the entire study (through, the maintenance 12-week period). Overall, 13 subjects (30%) dropped out of the study because of medication side effects.

Patients were eligible if they met the following inclusion criteria: (1) CPP of at least 6 months duration diagnosed by a gynecologist in the outpatient Pelvic Pain Clinic at the University of North Carolina at Chapel Hill; (2) average pain of at least 4 on a visual analog pain scale filled out each day for 1 week; (3) age 18–60 years; and (4) having 1 of 3 types of CPP as diagnosed by a gynecologist who specializes in chronic pelvic pain. The 3 types of CPP included (1) diffuse abdominal pain (e.g., pain elicited during examination that was not localized and was without a single reproducible point or tender palpable spot)[14]; (2) neuropathic type pain (e.g., a mix of pain disorders initiated after surgery); and (3) vulvodynia pain (including vulvar vestibulitis). This categorization of pelvic pain has been previously shown to discriminate between types of CPP on mental and physical health.[14]

We recruited 2:1 vulvodynia-type CPP vs. the other subtypes based on our clinical experience with the CPP population and our previous work demonstrating that women with the vulvodynia subtype of CPP are less likely to have significant psychologic disturbance, sexual and/or physical abuse history, severe pain and other somatic complaints compared with women with other types of CPP. Additionally, we hypothesized that complex

abdominal pain likely has multiple causative contributions that unidimentional therapy would not address. Exclusion criteria included (1) active systemic diseases or disorders that would interfere with participation (e.g., heart, lung, kidney, liver, diabetes, cancer, stroke, seizures, psychotic disorders, malnutrition, surgery in previous 6 months, pregnancy, deafness, and blindness);, (2) current alcohol or substance dependence (e.g., marijuana, PCP, cocaine, heroin, LSD); (3) any use of valproic acid (Depakote) within 4 weeks of the study because of potential drug interaction with lamotrigine; (4) initialing use of antidepressant medications during the 1 month before the study; and (5) < 8 years of education, illiterate, and/or non-English speaking. Participants were allowed to continue taking analgesics (including TCAs, opioids and nonsteroidal antiinflammatory drugs) if they had been receiving them for at least 4 weeks before the study. Similarly, herbal remedies and alternative therapies such as massage and acupuncture were permitted to be continued if patients had been receiving them before study participation. Initiation of a new analgesic for use during the study was not permitted.

## Study Design

This 14-week study design included (1) Screening and Baseline Visit; (2) an 8-week Dose Escalation Phase; (3) a 3-week Dose Maintenance Phase; and (4) a 2-week Dose Tapering Phase. In total, there were 8 patient contact visits, including 5 office visits and 3 phone visits for each study participant. Questionnaire evaluation was performed at baseline and at the end of weeks 8 and 12.

**Screening and Baseline Visit—**Study participants were patients in the Pelvic Pain Clinic. This research protocol was approved by the University of North Carolina at Chapel Hill Institutional Review Board. All patients gave informed consent based on standard procedures by the Committee for the Protection of Human Subjects. Patients completed a pain diary card filled out during the week before the screening and baseline visit. Risks, benefits and side effects of administration of lamotrigine were discussed with all potential study participants, including the small risk for serious rash (Stevens-Johnson syndrome or toxic epidermal necrolysis), that have been reported secondary to exposure to lamotrigine. Patients who met all inclusion/exclusion criteria completed baseline questionnaires and interviews and were enrolled into the open-label study.

**Drug Dose Escalation Phase—**Treatment was initiated at a daily dose of 25 mg for 2 weeks, increased to 50 mg/day for 2 weeks, and subsequently to 100, 200, 300 and 400 mg/day, each dose for an additional week. The dosing schedule was once daily during the first 2 weeks and twice daily for the remaining 6 weeks.

**Drug Maintenance Phase—**The target maintenance dose was 400 mg/day (200 mg twice per day), although the minimum efficacious dose was 200 mg, if side effects did not permit further dose escalation.

**Dose Tapering Phase—**During the 2-week taper phase, study participants had the dose of lamotrigine reduced by 50% every 5 days until they were safely discontinued from the medication.

### Outcome Measures

We chose 5 primary outcome variables, as follows: (1) the McGill Pain Rating Index, consisting of 15 pain descriptors ranging from 0 (none) to 3 (severe) describing pain for the previous month[27]; (2) the McGill Visual Analog Scale (VAS) of overall pain intensity for the past month, ranging from 0 (no pain) to 10 (worst possible pain); (3) the McGill Pain Intensity Scale modified to rate pelvic pain from 0 (no pain) to 5 (excruciating); (4) the Hamilton Depression Rating Scale (HAM-D), a standard interview-based measure of depression[28]; and (5) the Hamilton Anxiety Rating Scale (HAM-A), a standard interview-based measure of anxiety.[29]

### Statistical Analysis

All statistical calculations were done using SAS version 8.2 (SAS Institute Inc., Cary, North Carolina). The main demographic and baseline characteristics are reported as means and SDs for continuous variables and as percentages for categorical variables. All outcome variables were approximately normally distributed. We compared all patients with CPP before and after receiving lamotrigine using a paired *t* test on the primary outcome variables. Comparisons were made from baseline to 8 weeks and from baseline to 12 weeks. We also examined changes within each type of CPP (e.g., diffuse abdominal, neuropathic, vulvodynia) using a paired *t* test from baseline to 8 and 12 weeks. We also used the general linear model with *t* test comparisons between the 3 subgroups of CPP patients to compare these groups on antidepressant use. Unpaired *t* tests were also used to compare study completers to noncompleters.

The primary aim of this study was to determine whether lamotrigine appears to have efficacy for patients with CPP, with a particular focus on vulvodynia, in terms of improvements in physical and psychological health.

**Power Analysis—**Our statistical power analysis was based on a paired *t* test assuming a standard difference (d) between paired outcomes over time of 0.60 (moderate effect size[30]), an SD of 1 for each outcome variable and a correlation of 0.50 between variables over time. We considered this difference to be a clinically meaningful change in symptoms and pain. With N = 31 (8-week analysis) and effect size d = 0.60, our power to detect this moderate difference was 0.90, assuming a 2-tailed test and alpha set at 0.05. With N=21 (12-week analysis) and effect size d = 0.60, our power was 0.74 using the same assumptions. Analyses within subtypes of CPP were limited to testing only large effects (d=0.70–0.80), yielding acceptable power (0.77–0.87) only for the vulvodynia pain group. The N of the other 2 groups required very large effect sizes (1.2) to have marginal power (> 0.75).

## Results

Table I describes the demographic information of our sample. The average age of the 31 patients completing 8 weeks of lamotrigine was 41 years (SD 12.6, range 23–67) and average educational level was 15.3 years (SD 1.8). All but 1 subject was Caucasian. The average dose of lamotrigine was 340 mg in those completing 8 weeks of treatment and 367

mg in those completing the 12-week maintenance phase. Types of CPP included vulvodynia pain (17), diffuse abdominal pain (7) and neuropathic pain (7).

The 10 participants who dropped out of the study after 8 weeks were not different in age, diagnosis, baseline depression or baseline pain compared with the 21 participants who completed 12 weeks of treatment. However, the dropouts tended to have on average 2 years less education ($p = 0.0009$). At the time of study entry, most patients were using concomitant medications, (ranging from 1 to 5 medications) such as antiinflammatories, antidepressants, narcotic pain medications and benzodiazepines. Approximately half (48.4%) of the patients were on antidepressant medication at baseline. Antidepressant use did not vary across type of CPP diagnosis ($\chi^2 = 1.92$, $p = 0.38$, $N = 31$). The baseline mean HAM-D score in the group as a whole was 12.3, which is consistent with a mild depressive disorder.[31]

When examining the group as a whole, we found that patients reported significant reductions on the McGill Pain Rating Index, McGill Visual Analog Scale and overall pain intensity, pelvic pain intensity, Hamilton Depression and Hamilton Anxiety Scales at the 8- and 12-week visits compared to baseline (Tables II and III, respectively). As described in Table II, at 8 weeks of treatment with lamotrigine in the whole group, we found a robust treatment response with clinically and statistically significant reductions in pain (McGill Pain Rating Index, $p=0.003$; McGill pain intensity (VAS), $p < 0.0001$; pelvic pain intensity, $p < 0.0001$), improvement in mood (Hamilton Depression, $p = 0.002$) and anxiety symptoms (Hamilton Anxiety, $p = 0.02$). At 12 weeks of treatment (Table III), we saw a continued treatment response with further improvements in mood and anxiety symptoms (Hamilton Depression, $p = 0.001$; Hamilton Anxiety, $p = 0.004$).

When we further analyzed the data by the 3 subtypes of pelvic pain (Tables IV and V), we noticed a marked difference in response to treatment. The subjects in the vulvodynia pain group had robust reductions on all measures of pain at both the 8- and 12-week visits compared to baseline (Table IV and V, respectively). At the 8-week assessment, analyses of pain rating scales in the vulvodynia pain group were as follows: McGill Pain Rating Index, $p = 0.002$; McGill VAS overall pain intensity, $p = 0.0001$, and pelvic pain intensity, $p < 0.0001$. At the 12-week assessment, analyses of pain rating scales in the vulvodynia pain group were as follows: McGill Pain Rating Index, $p=0.015$; McGill VAS overall pain intensity, $p = 0.0003$; and McGill VAS pelvic pain intensity, $p = 0.002$. Analysis of mood and anxiety symptoms demonstrated nonsignificant reductions in depression and anxiety at 8 weeks (HAM-D, $p=0.113$; HAM-A, $p = 0.061$), with significant reductions in depression and anxiety symptoms at the 12-week visit (HAM-D, $p = 0.003$; HAM-A, $p=0.001$). These data are consistent with the slower onset of the mood-stabilizing effects of lamotrigine described in the literature.[32] In contrast, subjects with the diffuse abdominal pain subtype of CPP showed minimal response to lamotrigine on all measures. Those with the neuropathic pain subtype of CPP showed no significant changes on any measure; however, there were nonsignificant reductions in depression and anxiety equivalent to a > 1 SD change.

## Discussion

CPP is a heterogeneous disorder, with often poor treatment response and significant psychiatric co-morbidity. Our open-label pilot study suggests that the use of lamotrigine in the treatment of patients with CPP may be helpful in addressing both the pain and mood symptoms associated with this disorder. We found a clinically significant response to treatment with lamotrigine as evidenced by decreased pain scores (McGill Pain Rating Index, VAS pain intensity and pelvic pain) and improved mood and anxiety symptoms. In addition, we found that patients with the CPP subtype of vulvodynia demonstrated a particularly robust response that was clinically and statistically significant to treatment with lamotrigine in terms of both pain and mood symptoms. This is in contrast to patients with other types of pelvic pain (diffuse abdominal and neuropathic) who did not have a clinically significant reduction in pain. Of interest, despite the small number, patients with the neuropathic subtype of CPP had large drops in depression and anxiety (> 1 SD), albeit nonsignificant. With larger samples, these changes would likely have readied statistical significance.

Current theories suggest that CPP is a biopsychosocial disorder in which psychologic events such as sexual abuse and trauma may interact with structural and physiologic factors to produce symptoms.[9,16] These interactions determine how patients cope with their symptoms and how they respond to treatments, including psychologic as well as medical and surgical treatments. As described earlier, recent work has demonstrated that women with vulvodynia have better mental health and decreased rates of sexual and/or physical abuse history compared with women with other subtypes of pelvic pain.[10,11,14] Thus we hypothesize that a potential explanation for the robust response to treatment with lamotrigine seen in CPP patients with the subtype of vulvodynia may be due to differences in CNS pain regulatory mechanisms in this type of CPP vs. other subtypes. Patients with vulvodynia tend to have a more circumscribed type of pain, especially compared to those with diffuse abdominal pain. More diffuse-type pain may indicate greater dysregulation in central pain regulatory pathways[33,34] and thus may be less likely to respond to a unidimensional treatment modality.

Limitations of this pilot study included its open-label design with a lack of control group and a small sample size, particularly in the subtype analysis of CPP. Also, we had a dropout rate of 28%; however, most of these patients left for reasons unrelated to the medication. In addition, because our results are based on a single cohort from a referral-based pelvic pain clinic, we may have introduced a sample bias and limited the generalizability of our findings to a more diverse CPP population. The clinic tends to see patients who are treatment refractory. Responses of a less refractory patient group might be better than those in the current study. Despite these limitations, we have found highly favorable results from this pilot study that may provide the basis for a placebo-controlled clinical trial of lamotrigine with a larger sample of CPP patients.

In conclusion, the results of this pilot trial provide proof of concept for the use of psychotropic medications, in particular anticonvulsant medications with mood-stabilizing properties, such as lamotrigine, in the treatment of pelvic pain. Furthermore, treatment of

CPP needs to be specifically tailored based on the subtype of CPP (i.e., vulvodynia) because this may greatly influence the efficacy of a particular intervention.

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## References

1. Reiter RC. A profile of women with chronic pelvic pain. Clin Obstet Gynecol. 1990; 33:130–136. [PubMed: 2178830]
2. Howard FM. The role of laparoscopy in chronic pelvic pain: Promise and pitfalls. Obstet Gynecol Surv. 1993; 48:357–387. [PubMed: 8327235]
3. Howard FM. Chronic pelvic pain. Obstet Gynecol. 2003; 101:594–611. [PubMed: 12636968]
4. American College of Obstetricians and Gynecologist: Chronic Pelvic Pain: ACOG practice bulletin No. 51. Obstet Gynecol. 2004; 103:589–605. [PubMed: 14990428]
5. Jamieson D, Steege JF. Prevalence of dysmenorrhea, dyspareunia, pelvic pain, and irritable bowel syndrome in primary care practices. Obstet Gynecol. 1996; 87:55–58. [PubMed: 8532266]
6. Jamieson DJ, Steege JF. The association of sexual abuse wish pelvic pain complaints in primary care population. Am J Obstet Gynecol. 1997; 177:1408–1412. [PubMed: 9423743]
7. Mathias SD, Kuppermann M, Liberman RF, et al. Chronic pelvic pain: Prevalence, health related quality of life and economic correlates. Obstet Gynecol. 1996; 87:321–327. [PubMed: 8598948]
8. Dersh J, Polatin PB, Gatchel RJ. Chronic pain and psychopathology: Research findings and theoretical considerations. Psychosom Med. 2002; 64:773–786. [PubMed: 12271108]
9. Meltzer-Brody S, Leserman J, Zolnoun D, et al. Trauma and posttraumatic stress disorder in women with chronic pelvic pain. Obstet Gynecol. 2007; 109:902–908. [PubMed: 17400852]
10. Reed BD, Haefner HK, Punch MR, et al. Psychosocial and sexual functioning in women with vulvodynia and chronic pelvic pain: A comparative evaluation. J Reprod Med. 2000; 45:624–632. [PubMed: 10986680]
11. Bodden-Heidrich R, Kuppers V, Beckmann MW, et al. Psychosomatic aspects of vulvodynia: Comparison with the chronic pelvic pain syndrome. J Reprod Med. 1999; 44:411–416. [PubMed: 10360252]
12. Marcus DA. Headache and other types of chronic pain. Headache. 2003; 43:49–53. [PubMed: 12864758]
13. Zondervan KT, Yudkin PL, Vessy MP, et al. The community prevalence of chronic pelvic pain in women and associated illness behavior. Br J Gen Pract. 2001; 51:541–547. [PubMed: 11462313]
14. Leserman J, Zolnoun D, Meltzer-Brody S, et al. Identification of diagnostic subtypes of chronic pelvic pain and how subtypes differ in health status and trauma history. Am J Obstet Gynecol. 2006; 8:554–560. [PubMed: 16769027]
15. Gunter J. Vulvodynia: New thoughts on a devastating condition. Obstet Gynecol Surv. 2007; 62:812–819. [PubMed: 18005458]
16. Zolnoun D, Hartmann K, Lamvu G, et al. A conceptual model for the pathophysiology of vulvar vestibulitis syndrome. Obstet Gynecol Surv. 2006; 61:395–401. [PubMed: 16719941]
17. Haefner HK, Collins ME, Davis GD, et al. The vulvodynia guideline (review). J Low Genit Tract Dis. 2005; 9:40–51. [PubMed: 15870521]
18. Reed BD. Vulvodynia: Diagnosis and management. Am Fam Physician. 2006; 73:1231–1238. [PubMed: 16623211]
19. Xie X, Lancaster B, Peakman T, et al. Interaction of the antiepileptic drug lamotrigine with recombinant rat brain type IIA $Na^+$ channels and with native $Na^+$ channels in rat hippocampal neurons. Pflugers Arch. 1995; 430:437–446. [PubMed: 7491269]

20. Woolf CJ, Thompson SWN. The induction and maintenance of central sensitization is dependent on*N*-methyl-aspartic acid receptor activation: Implications for post-injury pain hypersensitivity states. Pain. 1991; 44:293–298. [PubMed: 1828878]
21. Jose VM, Bhansali A, Hota D, et al. Randomized double-blind study comparing the efficacy of safety of lamotrigine and amitriptyline in painful diabetic neuropathy. Diabet Med. 2007; 24:377–383. [PubMed: 17335465]
22. Vinik AI, Tuchman M, Safirstein B, et al. Lamotrigine for treatment of pain associated with diabetic neuropathy: Results of two randomized, double-blind, placebo-controlled studies. Pain. 2007; 128:169–179. [PubMed: 17161535]
23. Eisenberg E, Lurie Y, Braker C, et al. Lamotrigine reduces painful diabetic neuropathy. Neurology. 2001; 57:505–509. [PubMed: 11502921]
24. Simpson DM, Olney R, McArthur JC, et al. Neurology: A placebo-controlled trial of lamotrigine for painful HIV-associated neuropathy. Neurology. 2000; 54:2115–2119. [PubMed: 10851374]
25. Simpson DM, McArthur JC, Olney R, et al. Lamotrigine for HIV-associated painful sensory neuropathies: A placebo-controlled trial. Neurology. 2003; 60:1508–1514. [PubMed: 12743240]
26. Krymchantowski AV, Bigal ME, Moreira PF. New and emerging prophylactic agents for migraine. CNS Drugs. 2002; 16:611–634. [PubMed: 12153333]
27. Melzack R. The short-form McGill Pain Questionnaire. Pain. 1987; 30:391–197.
28. Hamilton M. Development of a rating scale for primary depressive illness. Br J Soc Clin Psychol. 1967:278–296. [PubMed: 6080235]
29. Hamilton M. The assessment of anxiety states by rating. Br J Med Psychol. 1959; 32:50–55. [PubMed: 13638508]
30. Cohen, J. Statistical Power Analysis for the Behavioral Sciences. Second edition. Hillsdale NJ: L Erlbaum Associates; 1988. p. 531-535.
31. Olsen LR, Jensen DV, Noerholm V, et al. The internal and external validity of the Major Depression Inventory in measuring severity of depressive states. Psychol Med. 2003; 33:351–356. [PubMed: 12622314]
32. Silverstone PH, Silverstone T. A review of acute treatments for bipolar depression. Int Clin Psychopharmacol. 2004; 19:113–124. [PubMed: 15107653]
33. Diatchenko L, Slade G, Nackley A, et al. Genetic basis for individual variations in pain perception and the development of a chronic pain condition. Hum Mol Genet. 2005; 14:135–143. [PubMed: 15537663]
34. Diatchenko L, Wackley A, et al. Idiopathic pain disorders: Pathways of vulnerability. Pain. 2006; 123:226–230. [PubMed: 16777329]

**Table I**

Demographic Characteristics of Women with CPP at Baseline and After 8 and 12 Weeks of Treatment

| Demographic characteristic | 8-week completers (N = 31) | 12-week completers (N = 21) |
|---|---|---|
| Age (yr) | 41.0 | 39.90 |
| Education (yr) | 15.3 | 15.95 |
| Race (% white) | 95% | 100% |
| Average dose of lamotrigine (mg) | 340 | 367 |
| Diagnostic subtype of CPP by group | | |
| Vulvodynia | 17 | 13 |
| Diffuse abdominal | 7 | 4 |
| Neuropathic pain | 7 | 4 |

**Table II**

Comparison of Means at Baseline vs. 8 Weeks of Treatment Total Group (N=31)

| | Baseline | | 8 Weeks of treatment | | Paired *t* test |
|---|---|---|---|---|---|
| **Scale** | **Mean X** | **(SD)** | **Mean X** | **SD** | **p Value** |
| McGill Pain Rating Index | 19.46 | 10.86 | 13.66 | 9.46 | 0.003 |
| Overall pain intensity | 7.16 | 2.03 | 4.97 | 2.52 | < 0.0001 |
| Overall pelvic pain | 3.35 | 0.95 | 2.23 | 1.12 | < 0.0001 |
| Hamilton Depression | 12.26 | 5.85 | 9.26 | 4.67 | 0.002 |
| Hamilton Anxiety | 12.52 | 7.04 | 9.61 | 4.99 | 0.02 |

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**Table III**

Comparison of Means at Baseline vs. 12 Weeks of Treatment Total Croup (N=21)

| | Baseline | | 12 Weeks of treatment | | Paired *t* test |
|---|---|---|---|---|---|
| **Scale** | **Mean X** | **SD** | **Mean X** | **SD** | **p value** |
| McGill Pain Rating Index | 17.48 | 9.79 | 11.68 | 9.88 | 0.013 |
| Overall pain intensity | 6.67 | 2.15 | 4.10 | 2.64 | 0.0002 |
| Overall pelvic pain | 3.10 | 0.94 | 2.05 | 1.16 | 0.001 |
| Hamilton Depression | 11.29 | 4.58 | 6.96 | 5.26 | 0.001 |
| Hamilton Anxiety | 10.9 | 6.07 | 6.80 | 4.41 | 0.004 |

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**Table IV**

Change from Baseline to Week 8 (N = 31) (Comparison by Subtype of Pelvic Pain)[a]

| | Baseline | | 8 Weeks of treatment | | Paired *t* test |
|---|---|---|---|---|---|
| **Scale** | **Mean X** | **SD** | **Mean X** | **SD** | **p value** |
| McGill Pain Rating Index | | | | | |
| Vulvodynia | 15.66 | 8.30 | 9.59 | 6.44 | 0.002 |
| Diffuse abdominal | 28.67 | 8.58 | 19.06 | 11.70 | 0.134 |
| Neuropathic pain | 19.48 | 13.87 | 18.14 | 9.79 | 0.762 |
| Overall pain intensity | | | | | |
| Vulvodynia | 6.41 | 1.94 | 3.88 | 2.00 | 0.0001 |
| Diffuse abdominal | 8.14 | 1.46 | 6.14 | 3.02 | 0.145 |
| Neuropathic pain | 8.00 | 2.24 | 6.43 | 2.15 | 0.062 |
| Overall pelvic pain | | | | | |
| Vulvodynia | 3.12 | 0.93 | 1.71 | 0.85 | < 0.0001 |
| Diffuse abdominal | 3.71 | 0.76 | 3.00 | 1.41 | 0.283 |
| Neuropathic pain | 3.57 | 1.13 | 2.71 | 0.76 | 0.200 |
| Hamilton Depression | | | | | |
| Vulvodynia | 10.06 | 4.10 | 8.35 | 3.79 | 0.113 |
| Diffuse abdominal | 14.86 | 7.08 | 10.71 | 5.88 | 0.117 |
| Neuropathic pain | 15.00 | 6.78 | 10.00 | 5.54 | 0.061 |
| Hamilton Anxiety | | | | | |
| Vulvodynia | 10.59 | 5.16 | 8.20 | 3.66 | 0.061 |
| Diffuse abdominal | 13.14 | 9.26 | 11.43 | 7.09 | 0.667 |
| Neuropathic pain | 16.57 | 7.80 | 11.00 | 5.03 | 0.055 |

[a] n = 17 For vulvodynia, n = 7 for diffuse abdominal pain and n = 7 for neuropathic pain.

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**Table V**

Change from Baseline to Week 12 (N = 21) (Comparison by Subtype of Pelvic Pain)[a]

| | Baseline | | 12 Weeks of treatment | | Paired *t* test |
|---|---|---|---|---|---|
| **Scale** | **Mean X** | **SD** | **Mean X** | **SD** | **p value** |
| McGill Pain Rating index | | | | | |
| Vulvodynia | 15.00 | 9.26 | 8.77 | 6.77 | 0.015 |
| Diffuse abdominal | 24.42 | 7.22 | 20.30 | 11.07 | 0.418 |
| Neuropathic pain | 18.59 | 12.32 | 12.50 | 14.43 | 0.528 |
| Overall pain intensity | | | | | |
| Vulvodynia | 5.85 | 1.77 | 277 | 1.36 | 0.0003 |
| Diffuse abdominal | 8.00 | 1.83 | 6.50 | 2.52 | 0.406 |
| Neuropathic pain | 8.00 | 2.71 | 6.00 | 3.56 | 0.332 |
| Overall pelvic pain | | | | | |
| Vulvodynia | 2.85 | 0.80 | 1.62 | 0.77 | 0.002 |
| Diffuse abdominal | 3.50 | 1.00 | 275 | 1.26 | 0.215 |
| Neuropathic pain | 3.50 | 1.29 | 2.75 | 1.71 | 0.520 |
| Hamilton Depression | | | | | |
| Vulvodynia | 10.46 | 4.05 | 6.08 | 4.27 | 0.003 |
| Diffuse abdominal | 10.50 | 4.12 | 10.50 | 6.66 | 1.000 |
| Neuropathic pain | 14.75 | 6.13 | 6.27 | 6,83 | 0.060 |
| Hamilton Anxiety | | | | | |
| Vulvodynia | 11.00 | 5.76 | 6.42 | 4.83 | 0.001 |
| Diffuse abdominal | 7.00 | 4.97 | 8.50 | 3.11 | 0.673 |
| Neuropathic pain | 14.50 | 7.14 | 6.25 | 4.79 | 0.098 |

[a] n = 13 For vulvodynia, n = 4 for diffuse abdominal pain and n = 4 for neuropathic pain.