National Vulvodynia Association

NVA News

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Pharmacologic Options for Vulvodynia: Are they Effective?

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NVA: Do existing treatments for vulvodynia relieve pain in the majority of patients?

CB/GB: Numerous treatments have been used to treat vulvodynia, including oral medications (antidepressants, anticonvulsants), topical medications (lidocaine, anti-inflammatories), physical therapy, nerve blocks and surgery (e.g., vestibulectomy). No single treatment, however, has been shown to relieve or ameliorate pain in the majority of women with vulvodynia. A multidisciplinary approach, incorporating a combination of treatments and management interventions, is likely to be more effective than a single treatment. Therefore, future studies on treatment efficacy should employ several management strategies rather than one intervention. Until recently, few studies compared treatment outcome in different subgroups, but many experts suggest that women with a certain vulvodynia subtype (e.g., localized versus generalized, provoked versus

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NVA-Funded Research: What Have We Learned?

To date, the NVA has awarded over $1 million in research grants. The grants awarded by the NVA provide scientists with the opportunity to gather critical pilot data, which is essential to secure funding from larger institutions, such as the National Institutes of Health (NIH). Below is a summary of select studies and their results.

Yitzchak Binik, Ph.D.

Dr. Binik and his McGill University colleagues were awarded an NVA research grant to investigate the relationship between chronic recurrent candidiasis (yeast) infection and provoked vestibulodynia (PVD) in an animal model. Previously, many women with PVD had reported recurrent episodes of yeast infection. This observation led some researchers to speculate that chronic candidiasis infection, in which there is prolonged irritation of the vulvovaginal mucosa, might

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unprovoked) may be more responsive to certain therapies.

NVA: What is the most common first-line treatment for vulvodynia?

CB/GB: Based on their efficacy in the treatment of other chronic pain conditions, oral tricyclic antidepressants (TCAs) have been widely used as first line pharmacologic treatment for all subtypes of vulvodynia. Among the TCAs, amitriptyline has been prescribed most often, initially at a dose of 10 to 25 mg nightly, and then increased by 10 to 25 mg weekly (Haefner 2005). Dosage should be increased until the pain level is controlled or side effects are intolerable. Maximum dosage should not exceed 150 mg daily. Side effects associated with amitriptyline include sedation, constipation, dry mouth, cognitive dysfunction and sexual dysfunction. Women with vulvodynia who also suffer from depression may find higher doses effective (Reed 2006). Other TCAs, such as desipramine and nortriptyline, have been used because they have a lower incidence of side effects. Titration and maximum dosage is similar to amitriptyline, but desipramine is often taken in the morning because of its stimulating properties.

NVA: How long should you stay on this treatment if it's not relieving your symptoms?

CB/GB: It is unclear how long a woman should remain on a TCA, because the duration of treatment has ranged from one to 30 months in multiple studies. Although a TCA may be prescribed indefinitely until an alternative is considered, an adequate trial would be 150 mg of a TCA for three months, if the drug is tolerated (De Andres 2015, Reed 2006). Keep in mind that it takes a few months to reach a 150 mg dose, which means that one should stay on the medication for about five or six months to assess maximum efficacy.

NVA: What have research studies concluded about this type of treatment?

CB/GB: In the medical literature, five studies have evaluated the efficacy of an oral TCA: two randomized controlled trials (RCTs) and three case series. An RCT is the gold standard, because it compares the results of a treatment group to a control (placebo) group. Both RCTs of tricyclic antidepressants did not find positive results, i.e., the treatment provided minimal relief of vulvar pain. These studies, however, included women with localized and generalized vulvodynia, as well as women with provoked and unprovoked vulvodynia, so treatment efficacy for specific subgroups is unknown.

The first RCT had three arms: low dose amitriptyline (10-20 mg); 10-20 mg of amitriptyline plus a topical steroid; and a self-management program, which included cognitive behavioral techniques, physical therapy and sex therapy. Fifty-three women with provoked, unprovoked and mixed vulvodynia symptoms participated for 12 weeks. Although the study

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The National Vulvodynia Association is a non-profit organization that strives to improve women's quality of life through education, support, advocacy and research funding.

The NVA is not a medical authority and strongly recommends that you consult your own health care provider regarding any course of treatment or medication.

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found no significant difference in pain relief among the three groups, as measured pre- and post-treatment by the McGill Pain Questionnaire, significant within-group pain relief occurred in the self-management group (Brown 2009).

In the next RCT, 133 women with provoked vestibulodynia were assigned to one of four groups: (i) 25 mg oral desipramine (TCA with milder side effects than amitriptyline) plus a topical placebo cream, (ii) desipramine plus topical 5% lidocaine, (iii) lidocaine plus placebo tablets, and (iv) placebo tablets and placebo cream. Reduction of pain during a tampon test, the study's primary outcome measure, was not significantly different in the three treatment arms and control group. Similarly, no significant differences were found in self-reported pain and pain with intercourse (Foster 2010). In contrast, a prospective case series of 209 women with mixed vulvodynia symptoms, generalized and localized, receiving amitriptyline or desipramine of an unknown dose, found that the TCA-treated group reported greater pain relief than the control group.

One retrospective case series of 33 women with generalized or localized vulvodynia also reported that amitriptyline or desipramine resulted in complete pain relief in 47 percent of patients. Another retrospective series, however, found no improvement in pain in 20 women with generalized vulvodynia who took 40-60 mg amitriptyline daily. Unfortunately, pain measures were not identified in either study.

Only two studies have evaluated the use of topical TCAs for vulvodynia. In a prospective, non-randomized study of 150 women with provoked vestibulodynia (PVD), who used topical amitriptyline for 12 months, 56 percent reported pain relief. A retrospective study of 38 women who used a combination of 2% amitriptyline and 2% baclofen cream found that 53 percent reported symptoms as "very much improved" after eight months of treatment (De Andres 2015).

NVA: Why do some doctors prefer to prescribe an anticonvulsant as a first line treatment?

CB/GB: Some clinicians prefer to prescribe anticonvulsants, because they may have a lower incidence of side effects. Anticonvulsants, similar to TCAs, have been used to treat other chronic pain conditions. Currently, the most commonly used anticonvulsant is gabapentin (Neurontin). It is generally started at 300 mg daily for three days, increased to 300 mg twice per day for three days, and then 300 mg three times a day (Haefner 2005). It can be further increased gradually to a maximum of 3600 mg per day. Ideally gabapentin is given three times daily, but if the patient is unable to comply, it can be taken twice per day. When using higher doses, however, a three times daily regimen should be followed so each dose does not exceed 1200 mg. The most common side effects of gabapentin are drowsiness, nausea, headaches and dizziness. A newer sustained-release formulation, Gralise, is available for twice-daily dosing and is considered to have fewer side effects than immediate-release gabapentin.

Despite their widespread use, even less efficacy data is available on this class of drugs than on TCAs, with only three retrospective case series conducted to date. Among 601 women with generalized unprovoked vulvodynia, 64 percent experienced adequate resolution of symptoms with gabapentin. Although it is assumed that anticonvulsants have a more tolerable side effect profile, 11 percent of the women discontinued use of the drug due to adverse effects. Treatment with gabapentin also provided “significant improvement" using a visual analogue scale in a case series of 73 women with unspecified vulvodynia.

Use of 2-6% topical gabapentin in 51 women with PVD and generalized vulvodynia resulted in 80 percent reporting “at least 50 percent improvement” and 29 percent reporting “complete improvement.” Even though these studies reported positive findings, there were no control groups. A multicenter double-blind RCT is currently underway to determine whether oral gabapentin is effective in the treatment of PVD (Brown 2013).

NVA: Is there research data on the efficacy of other anticonvulsants in the treatment of vulvodynia?

CB/GB: From the literature, it appears that only one study has evaluated another anticonvulsant in the

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treatment of vulvodynia. In an open-label study of lamotrigine, 43 women with vulvodynia were given the medication and reported significant reduction in pain, anxiety and depression after eight weeks of treatment. Since it was an open-label study, the results are difficult to interpret.

NVA: How do topical medications lead to pain relief?

CB/GB: Topical medications reduce pain in a number of ways. Lidocaine, a local anesthetic, when applied to the painful area, works by temporarily blocking the pathway of pain signals along superficial nerve branches in that area. It achieves this by stopping the sodium from entering the nerve ending at the pain site, preventing an electrical signal from building up and passing along the nerve fibers to the brain. Corticosteroid topicals relieve pain by interfering with the production of cytokines, e.g., interleukin, which cause inflammation. Botulinum toxin A (Botox), a neuromuscular blocking agent, reduces the number of neurotransmitters that notify the brain that the body is in pain, and thus reduces muscle spasms. (Botox is injected into the intra-levator muscles.) Capsaicin, a transient receptor potential vanniloid 1 (TRPV1) agonist, works by first stimulating, and then decreasing, the transmission of pain signals in the body. Upon first application, pain increases, but it usually decreases afterwards. Typically, capsaicin is applied over several weeks with decreased dosing over time.

NVA: Because topical lidocaine is an anesthetic, it is widely prescribed to vulvodynia patients. Is it an effective treatment?

CB/GB: Topical lidocaine is the most common anesthetic prescribed in the treatment of vulvodynia (Haefner 2005). Three studies have evaluated the efficacy of topical lidocaine in PVD, including one double-blind placebo-controlled RCT, one RCT and one prospective case series. Foster (2010) found there was no difference between topical 5% lidocaine cream, oral desipramine, lidocaine plus desipramine, and matching placebo groups in pain reduction on the tampon test or during intercourse in 133 women with PVD. Similarly, Danielsson's RCT found no difference in vestibular tenderness (as measured by a vulvar algesiometer), quality of life, or sexual function among 46 PVD-affected women receiving either topical 5% lidocaine ointment or electromyographic (EMG) feedback. Zolnoun (2003) reported that 54 percent of women had at least a 50 percent reduction in dyspareunia (painful sexual intercourse) following the overnight use of topical 5% lidocaine ointment in a case series of 69 subjects. The modest benefit that was reported may be due to the prolonged exposure to lidocaine, which may be necessary to desensitize the vestibular nerves (De Andres 2015).

Although the level of evidence for the efficacy of topical lidocaine is minimal, its low cost and safety profile make it a potential option for women who may want to use it when there will be pressure (or touch) to the vulvar area, such as before a pelvic examination or with sexual penetration. Also, it can be a management strategy for those who prefer not to take oral medication.

NVA: Some doctors recommend capsaicin. Do research studies find it provides pain relief?

CB/GB: One prospective and one retrospective case series have evaluated the efficacy of capsaicin cream in women with PVD. In the prospective study of 33 women receiving 0.05% capsaicin cream, dyspareunia improved in 59 percent and there was no improvement in 41 percent. Steinberg conducted a retrospective case series of 52 women with PVD and found that the application of 0.025% capsaicin cream resulted in "significant improvement" on the touch test of Marinoff's dyspareunia scale. In both studies, however, lidocaine was applied prior to the capsaicin to prevent irritation/burning upon administration, so it is impossible to isolate the effect of capsaicin.

Although very infrequent, capsaicin may cause serious burns at the application site, and in rare cases, hospitalization has been required. Because of the potential for significant adverse local skin events, including an increase in pain intensity, and the fact that only two

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published non-controlled studies have been conducted, capsaicin is not recommended as a standard treatment for PVD.

NVA: Is it common for doctors to use injectable anesthetics for a) vestibulodynia and/or b) generalized vulvodynia?

CB/GB: Injectable anesthetics may be used to treat both vestibulodynia and generalized vulvodynia. Doctors administer injectable anesthetics when other treatment options have been ineffective, side effects to medications have been intolerable, or a woman feels uncomfortable taking an oral medication on a chronic basis. They also may be considered as adjunctive treatment.

NVA: What is the rationale for this type of treatment? Are any injectable anesthetics effective in treating vulvodynia?

CB/GB: Injectable anesthetics provide the most direct route of delivery of a pharmacological agent to the painful area. When injected near the peripheral nerves, they interrupt the pain signals from the vulva to the spinal cord.

The efficacy of anesthetic injections has been evaluated in three prospective case series. Rapkin performed a study combining three anesthetic injections: an epidural (using ropivacaine), a pudendal nerve block using bupivacaine, and infiltration of the vulvar vestibule using bupivacaine. Of 27 women with PVD, 46 percent were considered responders on the McGill Pain Questionnaire (MPQ), 57 percent by self-report and 41 percent from vulvalgesiometer results (a mechanical device that measures vestibular pain). Additionally, McDonald and Rapkin reported similar findings on the MPQ using the same anesthetics and methods of administration in 26 women with generalized vulvodynia.

In another prospective case series of 22 women with PVD, Murina et al. found that a combination of lidocaine and the steroid, methylprednisolone, led to "some improvement" in 68 percent and "complete improvement" in 32 percent (De Andres 2015). Larger controlled trials are needed to determine whether injectable anesthetics, with or without steroids, are effective in the treatment of vulvodynia.

NVA: Some doctors use Botox for the treatment of vulvodynia. What is the rationale for its use?

CB/GB: Botox, or botulinum, inhibits the release of glutamate, a neurotransmitter, and substance-P, a peptide involved in transmitting pain, from nociceptors (pain receptors). Inhibition of these nociceptors may reduce peripheral and central sensitization associated with vulvodynia. In addition, Botox may decrease spasm in the pelvic floor muscles.

NVA: Have studies found Botox to be effective?

CB/GB: The efficacy of botulinum, Type A (BTA) has been evaluated in a double-blind placebo controlled RCT and two case series. Petersen et al. found no difference between administration of 100 u BTA versus placebo in level of pain, quality of life and sexual function in 64 women with PVD. In contrast, a prospective case series of 20 women with PVD, by Pelletier et al., found that 80 percent of women reported an improvement in pain and 72 percent were able to have sexual intercourse following a dose of 100 u of BTA. Quality of life and sexual function also improved. Similarly, lower doses of Botox (35-50 u) were found to significantly reduce pain and oral medication use, and improve quality of life, in a retrospective study of 19 women with PVD. Because the RCT showed no improvement with BTA compared to placebo, and because of its expense, complexity of the medical procedure, and potential for serious side effects, Botox is not recommended as a first-line treatment for PVD. It may be useful, however, in combination with pelvic floor physical therapy (De Andres 2015).

NVA: What evidence indicates that vulvodynia may be an inflammatory condition?

CB/GB: Vulvodynia may be an inflammatory condition caused by a traumatic injury of the vestibular mucosa, which then leads to peripheral and central

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sensitization. There is strong evidence of increased proliferation of nerve fibers in vestibular tissue, as well as increased perception of systemic pain in women with PVD. This may involve the existence of polymorphisms (variations) in genes encoding for cytokines and interleukin receptor, and the mannan-binding lectin (MBL) gene. These polymorphisms result in a stronger inflammatory response and can make affected women susceptible to vulvodynia.

NVA: What is the mechanism of action of corticosteroids? Are they effective in treating vestibulodynia or generalized vulvodynia?

CB/GB: Research has shown that tissue levels of interleukin (IL-β), an inflammatory substance, are significantly higher in the hymen region of the vestibule in women with PVD. More recent findings suggest that the vulvar vestibule possesses unique inflammatory/immunologic responsiveness in all women and that vulvodynia reflects an extreme example of a natural phenomenon. Corticosteroids are anti-inflammatory agents that reduce production of certain interleukins.

Three RCTs have been conducted evaluating the efficacy of topical corticosteroids in the treatment of PVD. Munday compared a super high-potency corticosteroid (clobetasol 0.05%) to a low-potency corticosteroid, hydrocortisone 0.5% (placebo) ointment, in a crossover study of 22 women with PVD. Seventy-three percent of women improved on clobetasol, while 60 percent improved with hydrocortisone cream. Desrochers et al. found significant improvement in pain and sexual function with both a 1% corticosteroid cream and cognitive behavior therapy in 111 women with PVD (De Andres 2015). In a three-treatment arm study of 53 women with PVD, Brown found no difference between groups receiving (i) amitriptyline, (ii) amitriptyline and 0.1% triamcinolone cream (medium potency), and (iii) self-management (Brown 2009). Thus, there is no evidence to suggest that corticosteroids are an effective treatment for PVD.

NVA: Is interferon still being used to treat vulvodynia? If so, why?

CB/GB: Currently, interferon is seldom used to treat vulvodynia, because studies in the 1990s showed a lack of efficacy. Bornstein compared total perineoplasty to partial perineoplasty plus interferon (IFN-α2b) infiltration in 19 women with PVD, and found that 67 percent of those undergoing total perineoplasty had complete pain relief compared to 70 percent of those having partial perineoplasty plus IFN-α2b. In a prospective case series of 55 women with PVD, 49 percent of women treated with IFN-α had substantial or partial improvement in coital pain and vestibular tenderness. Of the 19 who elected to have surgery, 84 percent experienced substantial improvement and 11 percent had partial improvement in symptoms (De Andres 2015).

NVA: Are there any other effective anti-inflammatory agents?

CB/GB: Two other anti-inflammatory agents have been investigated, but as with corticosteroids, there is scant support of their efficacy. In a double-blind, placebo-controlled RCT of 34 women with PVD, Nyirjesy found that 54 percent of women receiving cromolyn cream, a mast cell stabilizer, compared to 38 percent who received placebo cream, had at least a 50 percent improvement in dyspareunia and vestibular tenderness. In a more recent RCT of 30 women with PVD, Donders found that lysate skin cream, containing a variety of anti-inflammatory cytokines, produced a significant, although modest, reduction in vestibular sensitivity and intercourse pain compared to placebo cream (De Andres 2015).

NVA: What is enoxaparin and how is it administered?

CB/GB: Enoxaparin is low molecular weight heparin, an anticoagulant, with anti-heparinase properties. Since there is an increased presence of the enzyme heparinase in the vestibule of women with vulvodynia, enoxaparin may treat vulvodynia by blocking its activity. Enoxaparin is self-administered subcutaneously in the abdomen daily.

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Urgent Appeal to Vulvodynia Patients

Although many researchers are working diligently to discover the causes of vulvodynia, we need to determine which medications doctors currently prescribe are effective in relieving vulvar pain. These medications include oral antidepressants and anticonvulsants, and topical medications, such as anesthetics, anti-inflammatories and compounded creams or gels with one or more active ingredients, e.g., amitriptyline and baclofen. In addition, we need to determine the efficacy of specific nerve blocks and pelvic floor physical therapy techniques. The only way clinical researchers can determine which treatments are actually effective is through randomized controlled trials, in which patients are randomly assigned to either a treatment or control (no treatment) group.

There have been very few randomized controlled treatment trials with vulvodynia patients. One significant problem is that clinical researchers cannot find enough willing subjects. In spite of the fact that the NVA advertises studies and researchers distribute flyers etc., not enough women with vulvodynia agree to participate in these studies. For example, even two pilot studies NVA funded were terminated at the halfway point, because the researchers could not recruit sufficient numbers of women with vulvodynia. Currently, we are funding an acupuncture study that is enrolling women very slowly, even though subjects are allowed to continue their medication while undergoing treatment. Unfortunately, NIH-funded clinical studies on vulvodynia experience similar difficulty recruiting subjects.

This situation is a crisis for women suffering from vulvodynia! Millions of women continue to take medications for many years that have not been proven to relieve vulvar pain. Some of these medications cause undesirable side effects, e.g., weight gain, but they can also cause serious long-term consequences. Consider the following example. One woman with severe vulvar pain was prescribed the anticonvulsant Trileptal (oxcarbamazepine) when she was 38. She took a moderate dose of 900 mg daily for 20 years, and was never sure whether it provided any pain relief. At her annual physicals, she had comprehensive blood tests. Everything was always normal. A few years ago, she read that some anticonvulsants can interfere with Vitamin D absorption, so she asked her doctor to test her Vitamin D level. As the woman feared, she was deficient in Vitamin D. Her internist then recommended a bone density test, because Vitamin D is essential for calcium absorption. Taking the Trileptal may not be the only contributor, but now she has moderate osteoporosis. She tapered the Trileptal as directed and discovered no change in her vulvar symptoms after she stopped it completely.

Sometimes you have to take medications for your health, but at least there is scientific evidence that they lower your blood pressure, raise your hormone level, etc. Unfortunately, many women with vulvodynia say they can't tell if their medication is working, but they continue to take it. Why? Because just like the woman who continued to take Trileptal, they are afraid their pain will become worse without it.

Why share this discouraging news? Women suffering from vulvodynia desperately need each one of us who is able to volunteer for upcoming clinical research studies. It is a harsh reality, but women who have vulvodynia are partly responsible for the appalling lack of data on treatment effectiveness. If this situation continues, some of our dedicated researchers may decide to abandon vulvodynia as a field of study. We cannot sit by and let this happen.

What can you do?

Every few months, visit our website at www.nva.org/for-patients/participate-in-research/ to view a list of studies in need of participants. Also, check each NVA newsletter for study announcements. Please volunteer for the next study in your area, if you are eligible. Since most doctors rely on published research findings to decide what to prescribe, millions of women will benefit from your generosity!■

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NVA: Does enoxaparin relieve the symptoms of vulvodynia?

CB/GB: A recent study of 40 women with PVD showed that enoxaparin may have a modest effect in relieving symptoms of vulvodynia. Self-administration of 40 mg of enoxaparin daily for 90 days reduced dyspareunia compared to the placebo, a saline subcutaneous injection (28.9 percent versus 4.4 percent). Additionally, it reduced vestibular sensitivity to a Q-tip examination (29.6 percent versus 11.2 percent). Decreased vestibular sensitivity was correlated with a reduction in intraepithelial-free nerve fibers in the enoxaparin group, but not in the placebo group, suggesting that enoxaparin may reduce neuroproliferation and penetration of nerve fibers in the epithelium.

NVA: Why have some doctors prescribed nitroglycerin for vulvodynia patients and how is it administered? Is it an effective treatment?

CB/GB: Nitroglycerin has been prescribed for vulvodynia because it relaxes smooth muscle and has been used to treat other disorders characterized by muscle spasms, such as esophageal spastic disorders. It is administered as a 0.2% cream and applied directly to the vestibule at least three times per week and prior to sexual intercourse. One study found that 31 of 34 women with vulvodynia reported improvement in overall vulvar pain after four to six weeks of 0.2% nitroglycerin cream. In the 21 patients with pre- and post-treatment scores, there was a significant decrease in the frequency of overall painful episodes and all patients reported less pain during sexual activity (De Andres 2015). There is insufficient evidence to conclude whether nitroglycerin is effective. Women using this intervention should be monitored for headaches.

Summary

Various treatments for other chronic pain conditions have been used to treat women with vulvodynia, but no single treatment has been shown to relieve pain in the majority of affected women. It is possible that subgroups of women, such as those with localized versus generalized or provoked versus unprovoked, may be more responsive to certain therapies. It is important that future studies explore which subgroups are treatment responders. The use of multimodal therapy and novel agents also requires further exploration.

(Editor's note: The ongoing gabapentin clinical trial mentioned in this article is supported by grant number R01HD065740 from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) and the Office of Women's Health Research (OWHR).)

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CORRECTION: In the spring 2015 *NVA News*, there was a small error on page 12 of Dr. Deborah Coady's article. Regarding medical testing for diabetes, the sentence should have read, "To evaluate for diabetes or impaired glucose tolerance, the following medical tests are required: hemoglobin **A1c** blood level, glucose tolerance, and a metabolic and lipid panel."

RESEARCH

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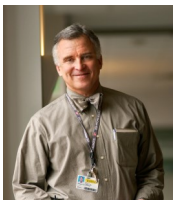
lead to abnormal pain transmission and vestibulodynia. Binik's study confirmed this hypothesis. He found that a subset of mice subjected to recurrent candidiasis infection developed allodynia (pain caused by stimuli that do not normally provoke pain) in the vulvar vestibule. Furthermore, they exhibited hyperinnervation in the vestibule, an increased number of pain-sensing nerve fibers. Long-lasting allodynia was also observed in a subset of mice that experienced a single, extended candidiasis infection upon repeated exposure to Zymosan, a mixture of fungal antigens. Both allodynia and hyperinnervation were present in this group at least three weeks after the resolution of the active infection and inflammation (Farmer 2011).

Nina Bohm-Starke, M.D., Ph.D.

Dr. Bohm-Starke was awarded an NVA research grant (matched by Danderyd Hospital in Sweden) to investigate whether a certain genetic variation is associated with general pain hypersensitivity in women with provoked vestibulodynia (PVD). Research had already determined that the guanosine triphosphate cyclohydrolase (GCH1) gene polymorphism affects overall pain sensitivity and the risk of developing a longstanding pain condition. Specifically, prior research found that specific single nucleotide polymorphisms (SNPs) in the GCH1 gene were associated with reduced pain sensitivity in humans (Heddini 2012).

In the current study, Dr. Bohm-Starke investigated whether the GCH1-gene polymorphism was associated with PVD, proposing that the pain-protective SNP combination might occur less frequently among affected women. Dr. Bohm-Starke explored associations between GCH1-polymorphism and vestibular and/or general pain sensitivity in women with PVD versus healthy controls. She also analyzed a possible interaction between the SNP combination and use of hormonal contraceptives. Her study did not find that GCH1-gene polymorphism contributes to the etiology of PVD. Bohm-Starke did, however, find one association between carrying the SNP combination and pain sensitivity. Among women with PVD currently receiving treatment, the SNP combination carriers who used hormonal contraceptives reported an increase in pain sensitivity. There was no change in pain sensitivity in women with PVD who were non-carriers, but used hormonal contraceptives. Some clinicians have noted that some patients with PVD improve after cessation of these hormones.

David Foster, M.D., M.P.H.



Dr. Foster, of the University of Rochester Medical Center, received one of the first NVA grants to investigate the neuro-inflammatory mechanisms of provoked vestibulodynia (PVD). Specifically, Dr. Foster studied the cytokine system, which mediates inflammation, and the neurokine system, which mediates pain. His results indicated that elevated pro-inflammatory cytokines produced by vulvar vestibule-specific fibroblasts (cells critical to wound healing) may cause PVD (Foster 2007). With NVA and other financial support, Dr. Foster gathered enough pilot data to submit a proposal to the NIH. His five-year NIH study, *Localized Vulvodynia Pathogenesis: Fibroblast, Yeast, and Melanocortin*, will conclude in 2017. The goal of this study is to identify a target cell that resides in painful regions of the vulva and responds to common stimuli with a heightened pro-inflammatory, pain-generating response. By identifying this cell, we will be closer to understanding the etiology of PVD and, ultimately, to more effective treatment and prevention measures.

Two years later, the NVA awarded a second grant to Dr. Foster to investigate the risk of PVD in the presence of two genetic variants, the interleukin-1 receptor antagonist (IL1RN) and melanocortin-1 receptor (MC1R), which affect chronic inflammation, pain and skin color. He conducted a retrospective, case-control study of 36 consecutive PVD cases and 69 pain-free controls (Foster 2004). The results of the study suggest that the risk of PVD may be increased in women with fair skin, and in women with pro-inflammatory genetic variants of IL1RN and MC1R. Women with

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both of these genetic variants may be at an even higher risk.

Catherine Leclair, M.D. and Terry Morgan, M.D.


Drs. Leclair and Morgan, of Oregon Health & Science University, were awarded a grant to assess whether pathologic pathways differ in women with primary versus secondary vestibulodynia (VBD). This analysis was based on archived vestibulectomy specimens from 88 premenopausal women with VBD (Leclair 2011). Histologic sections were stained to grade inflammation, and to highlight nerves, mast cells, estrogen receptor α and progesterone receptor. Specimens from primary VBD patients showed significant neural hypertrophy (increase in size of nerve cells) and hyperplasia (increase in number of nerve cells), and an increase in progesterone receptors compared to specimens from secondary VBD patients. It was, therefore, concluded that primary and secondary VBD have significantly different histologic features and that a decrease in progesterone receptors may be associated with secondary VBD. These findings suggest that primary and secondary VBD are distinct conditions.

Colin MacNeill, M.D.

Research has found that Surfactant Protein-A (SP-A) plays an essential role in providing protection against infection and that cytokines interact with immune system cells to help the body fight infection and regulate inflammatory responses. Dr. MacNeill, of Pennsylvania State College of Medicine, was awarded an NVA grant to measure the level of SP-A in vaginal fluid to determine if it is associated with levels of interleukins-1β and 8, two cytokines present in vaginal fluid at different points of the menstrual cycle. Little is known about innate vaginal immunity, including hormonal regulation of SP-A and the relationship of SP-A to known cytokine levels in vaginal fluids. Assays were carried out on vaginal fluid collected over three consecutive menstrual cycles from 10 healthy, naturally-cycling women who were sampled at three specific points in their cycles (MacNeill 2012). The three points were selected to assess whether SP-A is associated with distinct hormonal states. Both SP-A and cytokine levels were highest five to six days after menses and were significantly lower at ovulation and mid-luteal phase (one week after ovulation). This finding advances our knowledge of hormonal influences on innate immunity in the healthy female reproductive tract and provides a baseline for studying the role of surfactant proteins in initiating the inflammatory process in vulvodynia.

Linda McLean, Ph.D. and Caroline Pukall, Ph.D.


Drs. McLean (left) and Pukall (right), of Queen's University, were awarded an NVA research grant to study pelvic floor muscle function in women with provoked vestibulodynia (PVD). Specifically, the study's objectives were to determine whether women with and without PVD differ on measures of pelvic floor muscle function and to assess the impact of physical therapy treatment on these measures. Pelvic floor muscle function was evaluated using surface electromyography (SEMG) recordings and a digital intravaginal assessment in 11 women with PVD and 11 controls (Gentilcore-Saulnier 2010). The assessment was repeated in women with PVD after they had undergone eight physical therapy treatment sessions of manual therapy, biofeedback, electrical stimulation, dilator insertions and home exercises. The outcome measures were superficial and deep pelvic floor muscle SEMG activity in response to a painful pressure stimulus. Additionally, a pelvic floor muscle digital assessment evaluated muscle tone, flexibility, relaxation capacity, and strength. The results of the study showed that, at pretreatment, women with PVD had higher SEMG activity in their superficial pelvic floor muscles than the control group. No significant difference was found between the groups in the deep pelvic floor muscles. Both the PVD and control groups

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demonstrated a contractile response to the painful pressure stimulus that was significantly higher in the superficial pelvic floor muscles than in the deep muscles. As expected, the response was higher in the PVD group than in controls.

In women with PVD, the pelvic floor muscles had higher tone, decreased flexibility and less relaxation capacity than in the controls. Post-treatment improvement included reduced pelvic floor muscle responsiveness to pain, lower pelvic floor muscle tone, and improved vaginal flexibility and pelvic floor muscle relaxation capacity. After treatment, women with PVD no longer differed from controls on any of these measures.

Caroline Pukall, Ph.D.

Dr. Caroline Pukall, of Queen's University, was awarded an NVA research grant to examine differences between women with primary and secondary provoked vestibulodynia (PVD). Prior to this study, there had been a tendency to view all women with vestibulodynia as a homogeneous group. Pukall designed the study to determine whether women with primary versus secondary PVD demonstrated differences in etiology, pain characteristics and treatment outcomes. This study of 26 women (13 in each group) investigated multiple dimensions of pain and its functional effects (Sutton 2009). Subjects completed questionnaires and underwent a screening assessment, interview, standardized gynecological examination and quantitative sensory testing. Outcome measures included pain ratings of the gynecological examination, sitting during the interview and thermal sensory testing on the vulvar vestibule and dominant forearm.

Among the study's findings, women with primary PVD were more likely to have never given birth than women with secondary PVD, but were not significantly different on any other demographic variable or the gynecological examination. They also displayed less heat pain tolerance over the forearm and lower heat detection and pain thresholds in the vulvar vestibule. Furthermore, women with primary PVD reported impaired social and emotional functioning, and heightened anxiety regarding body exposure during sexual activity.

Andrea Rapkin, M.D.

Dr. Rapkin, of the UCLA Medical Center, was awarded an NVA research grant to perform a prospective non-controlled study assessing the efficacy of a novel combination of treatments in women with generalized vulvodynia: a caudal epidural block, transvaginal pudendal nerve block, and transperineal vulvar infiltration of local anesthetic agents. Twenty-six women underwent the regimen, which consisted of five treatment sessions and a follow-up contact two or three months afterwards. At that time, subjects were administered the McGill Pain Questionnaire, the Beck Depression Inventory and the Female Sexual Functioning Inventory. The study's results showed significant improvement in vulvar pain and depression, but not in sexual functioning (McDonald 2012).

Mark Tommerdahl, Ph.D. and Denniz Zolnoun, M.D.

Drs. Tommerdahl and Zolnoun of the University of North Carolina School of Medicine, Chapel Hill, were awarded an NVA grant to investigate underlying pain mechanisms in women with vulvodynia. This study's aim was to determine whether vulvodynia is associated with peripheral (local) nerve damage and/or central nervous system (brain and spinal cord) abnormalities. The investigators administered sensory tests to two fingers of the right hand in 12 women with vulvodynia and 20 age-matched controls (Zhang 2011). Their results indicate that women with vulvodynia who have experienced a long period of pain, and/or have unprovoked (spontaneous) symptoms, were more likely to have central nervous system involvement than control subjects

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or women with vulvodynia of short duration. It is essential to determine the underlying mechanisms of vulvodynia (peripheral, central or a combination of both) to develop effective pharmacologic and non-pharmacologic treatments.

Steven Witkin, Ph.D.

The precise mechanisms leading to allodynia and hyperalgesia (abnormally heightened sensitivity to pain) in women with vestibulodynia (VBD) remain incompletely defined. Recent evidence from the cancer field implicates the activity of serine proteases (enzymes that break down proteins) as a key intermediary in a prior unidentified mechanism in the induction of allodynia and hyperalgesia.

Dr. Witkin, of the Weill Medical College of Cornell University, received an NVA research award to investigate the concentration of certain proteases and protease inhibitors in the vaginal secretions of 76 women with VBD and 41 matched controls. He measured levels of proteases, kallikrein-5 and cathepsins B and S, as well as those of secretory leukocyte protease inhibitors (SLPI) and human epididymis protein-4 (HE-4). Dr. Witkin found markedly reduced concentrations of protease inhibitors, HE-4 and SLPI, in the vaginal samples of women with secondary, but not primary, VBD than in controls. The concentrations of both proteases were similar in all groups. Additionally, subjects with constant vulvar pain had lower levels of HE-4 and SLPI than women with intermittent vulvar pain or controls. Thus, increased pain sensitivity in women with secondary VBD, who have constant pain, may be related to insufficient vaginal protease inhibitor production (Jayaram 2015).

Denniz Zolnoun, M.D., M.P.H.

Many women with vulvodynia rely on compounded medications as a significant part of their treatment. The NVA awarded a grant to Dr. Denniz Zolnoun, of the University of North Carolina School of Medicine, to conduct a survey of compounding pharmacies in North Carolina. Her goal was to identify (i) the indications for use of compounded medications and (ii) the specific formulations dispensed by the pharmacies for treatment of vulvar pain. A survey was distributed to 653 non-chain pharmacies and 31 percent responded. She found that the most common use for compounded medication was for otolaryngological conditions (e.g., mouthwash and nasal irrigation), followed by dermatological conditions and vulvovaginal disorders. Of the medications compounded for gynecologic purposes, 73 percent of respondents produced bioidentical hormones and 70 percent made preparations for vaginal dryness. Additionally, almost 30 percent compounded medications for vulvar pain and 16 percent produced compounds for vulvovaginal infections (Corbett 2014). Currently, compounded medications for vulvar pain are not FDA-approved and, thus, insurance companies do not cover the cost.

(*Editor's note: To obtain a list of references, please contact the NVA administrator, Gigi Brecheen, via e-mail at gigi@nva.org or phone, 301-949-5114.*)■

Do you have Lichen Sclerosus?

We have been contacted recently by many more women with lichen sclerosus. We plan to feature an article on this dermatological condition in our next newsletter. We also print stories of women with chronic vulvar pain in the newsletter. If you were diagnosed with lichen sclerosus in the past few years, we'd like to hear about your experience. Please e-mail two or three double-spaced pages to Phyllis Mate at pmate@nva.org. Thank you.