

Treating GVD with Multilevel Nerve Blocks Results of an NVA-Funded Study

By Andrea Rapkin, MD

Dr. Rapkin is a professor of obstetrics & gynecology at the David Geffen School of Medicine at the University of California, Los Angeles (UCLA), and director of the UCLA Pelvic Pain Clinic.

Several years ago, Dr. John McDonald, professor and chairman of anesthesiology at the Harbor UCLA Medical Center, and I published the positive results of our study investigating the effectiveness of multilevel nerve blocks in women with Provoked Vestibulodynia (PVD) who had failed to respond to medical or surgical therapy (Rapkin 2008, also see *NVA News* Winter 2007). The block series significantly reduced women's pain scores, improved their sexual functioning and raised their vestibular pain threshold and tolerance levels. The protocol consisted of a series of multilevel local anesthetic injections to target three areas active in the maintenance of vulvar pain: i) the small nerve

fibers supplying sensation to the vulva, ii) the major peripheral nerves innervating the vulva (i.e., left and right pudendal nerves), and iii) the nerves exiting the sacral vertebra in the lower back/buttock area (S2-4). We subsequently applied for a NVA research grant to investigate whether this treatment was also effective in reducing vulvar pain severity in women with Generalized Vulvodynia (GVD). Additionally, we hoped to identify predictors of treatment response from women's medical histories, pelvic exams or responses to validated questionnaires on sexual function and

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NIH Establishes First Gynecologic Research Branch

An Interview with Alan Guttmacher, MD

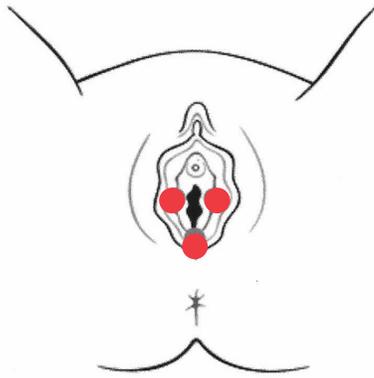
The National Institutes of Health (NIH) – our nation's medical research agency – is composed of 27 different Institutes and Centers, each of which has its own unique mission. Since 2000, Congress has charged the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) with funding and advancing scientific research on vulvodynia, along with several other benign gynecologic disorders such as endometriosis, uterine fibroids and pelvic floor disorders. Since coming to the NICHD in 2009, first as acting director, and a year later, assuming the position of director, Dr. Alan Guttmacher has led a series of “vision” conferences to identify research opportunities,

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Definitions and Types of Vulvodynia

Many different terms have been used to describe vulvodynia. As a result, confusion among patients and medical professionals is common. To encourage consensus and clarify terms used in this newsletter, we have provided a brief summary of the most current definitions and classification. For more detailed information, please visit http://learnprovider.nva.org/historical_overview.htm and http://learnprovider.nva.org/terminology_classification.html.

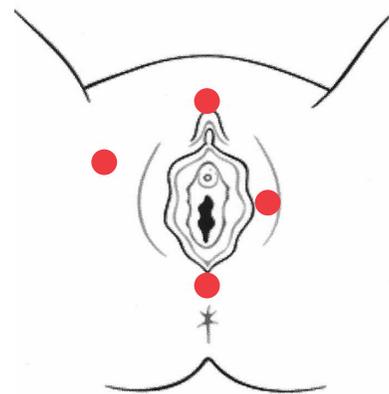
Vulvodynia is *chronic (more than three to six months) vulvar pain without an identifiable cause*. The location, constancy and severity of the pain vary among women. The two main subtypes of vulvodynia, which may co-exist, are:



Provoked Vestibulodynia (PVD)

(Previously: Vulvar Vestibulitis Syndrome)

Women with PVD only have pain in the vestibule (around the vaginal opening), that occurs during/after touch or pressure, e.g., with intercourse, tampon insertion, prolonged sitting. PVD is further classified as *primary (pain since the first attempt at penetration)* or *secondary (pain that starts after a period of pain-free penetration)*.



Generalized Vulvodynia (GVD)

(Previously: Dysesthetic or Essential Vulvodynia)

Women with GVD have spontaneous pain in multiple areas of the vulva. It is relatively constant, but there can be some periods of symptom relief. Activities that apply touch or pressure to the vulva, such as prolonged sitting or simply wearing pants, typically exacerbate symptoms.

NVA News

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The National Vulvodynia Association is a nonprofit organization that strives to improve women's lives 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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NIH Vulvodynia Research Investment Reaches Record High

For 15 years, the NVA has diligently advocated for an increased federal investment in vulvodynia research. In 2000, the National Institutes of Health (NIH) funded its first three vulvodynia studies, and for the next nine years, funding levels remained stagnant at approximately \$1 million annually. We couldn't be more pleased to report that, in a few short years, the NIH's annual investment in vulvodynia research has steadily climbed to \$12 million in 2012. Ten of the 17 current studies focus on vulvodynia's underlying mechanisms and treatment, and the other seven studies are investigating the disorder's relationship to other pain conditions. Additionally, six NIH Institutes/Centers are now investing in vulvodynia research, compared to just two in early years. This article summarizes the four projects that the NIH has funded in recent months. Summaries of all NIH-funded studies can be found on our website: www.nva.org/nih_funding.html.

Richard Gracely, PhD

*University of North Carolina - Chapel Hill
Center for Neurosensory Disorders*



The identification of vulvodynia's underlying disease mechanisms would greatly advance understanding of this prevalent disorder, and is a necessary step towards identifying and utilizing effective treatment strategies. The premise of Gracely's new research project, *A Necessary Multi-Parametric*

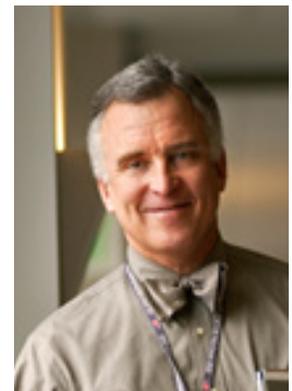
Evaluation of Vulvodynia, is that, similar to other pain disorders, vulvodynia results from localized events, such as vulvar skin injury and inflam-

mation, and secondary factors, such as sensory abnormalities in the brain and spinal cord. Additionally, individual factors, including genetic predisposition, environmental exposure and psychological distress, likely contribute to the disorder's development and/or maintenance. The current clinical exam for vulvodynia, which includes a cotton-swab (or Q-tip) test, does not, however, assess any of these important factors. Therefore, Gracely and his UNC colleagues are developing a novel vulvodynia assessment that will provide clinicians with the tools needed to identify specific dysfunctional nerve fiber types that contribute to a woman's vulvar pain and pelvic floor muscle abnormalities, as well as other critical individual factors specific to her pain presentation. Data generated from this study will enable the UNC group to differentiate women whose vulvodynia differs in its clinical presentation and underlying causes/mechanisms, as well as develop a logical classification system that can be used to identify these subgroups and guide the selection of individualized therapeutic strategies for each.

David Foster, MD, MPH

*University of Rochester
Dept. of Obstetrics and Gynecology*

In a series of prior studies, Foster and his research team have tested the hypothesis that the vulvar vestibule possesses unique inflammatory and immunologic responsiveness, and that vestibular pain experienced by women with Provoked



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NIH Investment

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Vestibulodynia (PVD) is an extreme example of a natural phenomenon. These studies have demonstrated that vestibular fibroblasts, i.e., connective tissue cells involved in wound healing, produce high levels of pro-inflammatory molecules (cytokines) after being exposed to irritants, such as yeast and yeast breakdown products. Although they've found high cytokine levels in vestibular fibroblasts from all women, they're markedly increased in women with PVD.

Foster's team has also found that certain genetic variations associated with the regulation of inflammation are more common in women with PVD, and are also associated with increased pro-inflammatory cytokine production in fibroblasts. These findings have led Foster to propose that PVD: i) arises in a region of the genital tract naturally predisposed to inflammation, i.e., the vestibule, ii) is initiated or triggered by specific irritants, such as yeast cell wall products, that induce a pro-inflammatory immune response, and iii) is more common in women carrying certain gene variations. Further, the *combination* of these factors is what leads to the induction of chronic vulvar pain.

In his new study, *Pathogenesis of Provoked Vestibulodynia*, Foster will investigate whether: i) pro-inflammatory fibroblasts segregate to painful areas of the vulva; ii) yeast or yeast products activate fibroblasts; iii) specific genetic variants modify this response; and iv) fibroblasts from vestibular tissue of women with a certain genetic variant, e.g., fair skin, demonstrate an altered immune response that can be reversed with a therapeutic agent. This is one step in Foster's long-term research goal, which is to delineate the various underlying mechanisms of PVD and then use this information to utilize therapies that specifically target each.

William Maixner, PhD, DDS

University of North Carolina - Chapel Hill
Center for Neurosensory Disorders

Growing evidence demonstrates that those suffering from one type of chronic pain often experience chronic pain elsewhere in the body. In his newest project, *Influences on the Transition from Acute to Chronic TMD and Related Pain*, Maixner and colleagues



will test the theory that specific combinations of genetic variants and risk factors cause acute pain to become chronic, as well as multiple pain disorders to develop. This premise is based on the findings of their prior first-of-its-kind multisite OPPERA project (Orofacial Pain, Prospective Evaluation and Risk Assessment), during which 3,200 healthy adults were prospectively followed and studied for several years. Seven percent developed temporomandibular disorders during this time, 86 percent of whom also developed one or more chronic pain conditions, including headache, low back pain, irritable bowel syndrome, vulvodynia and widespread body pain. In this second phase of OPPERA, Maixner's group will study 6,000 adults to evaluate these pain disorders as they first develop. They will measure genetic, physiological, psychological and clinical characteristics to determine why pain becomes persistent and why some people go on to develop multiple pain conditions.

Knowledge generated from this large national

See NIH INVESTMENT, page 10

Understanding Sex Therapy for Vulvodynia

By Nancy Levin McGrath, LICSW

Ms. McGrath is a licensed clinical social worker and AASECT-certified diplomate of sex therapy. She has a private practice in Brookline, Massachusetts, specializing in women's sexual pain issues through relationship, couples and sex therapy.

Many women who experience pain with sexual activity (“sexual pain”) need specialized treatment, but aren’t sure who to turn to or what treatment may involve. Sex therapy, in coordination with other treatments, may be a vital component of a comprehensive regimen for sexual pain. This article discusses what women can expect when consulting sex therapists.

Vulvodynia is a difficult condition to live with. There are few medical problems that have such a profound impact on how women feel about themselves. A woman's anticipation of sexual pain often leads to worry and anxiety – experiences that run counter to enjoying sexual activity. For others, months or years of living with chronic pain make it difficult for them to enter into or maintain positive, intimate physical connections with their partners. Some feel a loss of their “sexual self.”

A single woman with vulvodynia can feel particularly isolated and alone, and may be reluctant to disclose her condition, even to those who are closest to her. For example, I’ve had young clients who’ve been greatly distressed when friends or relatives suggest that they may have been sexually abused, which is usually not the case, after sharing their situation. A single woman may experience fear before discussing her condition with a new partner. A sex therapist can be proactive in helping a woman navigate these challenging conversations.

Often, men don’t realize that their partners with vulvodynia may worry excessively about their sexual relationships. In fact, a man may assume

that his partner's avoidance of sexual activity indicates a lack of interest in or concern about him and/or their sexual relationship. Men who come to treatment with their partners tend to be very loving and supportive, but simply don’t know how to help their partners or their relationships. Therapy helps to educate men about sexual pain problems, and they are usually relieved and satisfied when therapists give them specific action steps to improve their relationships. There is a saying in sex therapy, “The problem may be with one person, but the solution is with the couple.” Men certainly bring their own sexual histories, attitudes and life experiences to therapy. Therapists can help men with their side of the equation, as well as how they respond and react to difficult situations. My experience has been that men have a great ability to be patient and supportive when they see their partners taking steps to improve their physical and emotional health.

Longstanding sexual pain may cause a woman to fear opening up and dealing directly with this issue. Some couples are able to improve their sexual relationships on their own. The NVA’s online tutorial, *Everything You Need to Know about Vulvodynia*, available at <http://LearnPatient.NVA.org>, has many helpful suggestions, but for many couples, trying to deal with sexual pain on their own can prove too difficult and leave them feeling even more frustrated and defeated. These feelings are typically a sign that professional help is needed.

Perhaps a woman has gone to individual or couples

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Sex Therapy

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counseling in the past and isn't sure how more counseling will help her to improve her situation with sexual pain. It is important to understand that sex therapy, which is another form of talk therapy, involves a different approach that is highly specific and directed.

Finding a Therapist

Sex therapists come from several different professional disciplines, including clinical social work, clinical psychology and psychiatry. A woman can get assistance in finding a local sex therapist by asking her gynecologist or primary care provider for a referral, or by visiting the American Association of Sex Educators, Counselors and Therapists (AASECT) website, www.AASECT.org, and clicking on "Locate a Professional." Ideally, a good sex therapist has basic training in psychotherapy, specialized training in sexuality, which usually involves some combination of academic and supervised clinical work, and a commitment to learning about and treating vulvodynia.

When calling prospective therapists, a woman should feel free to ask about credentials and licensing, including specific subspecialty training and the length of time treating vulvodynia patients. She should also inquire about fees and whether treatment will be covered by her health insurance. A woman should keep in mind that the first sex therapist she visits may not end up being the best match. Although feeling uncomfortable at first is common, it may also signal a poor match. Many women, however, are actually relieved to have found their way to sex therapy and don't have these concerns.

The First Session

To begin, a sex therapist will take a detailed history to better understand how a woman's medical history, family background and previous experi-

ences may contribute to her current situation. It is important for a therapist to understand what the woman has done to date, both on her own and with her partner, to attempt to deal with sexual pain, as well as how she is managing in the present.

The Therapy Process

After taking a sexual history, it's important to establish appropriate and realistic goals. This involves helping the woman clarify her understanding of the problem and decide on the outcomes she'd like to work towards. Sex therapy is non-judgmental and therapists will not tell women what kind of sex life they should have or what their outcomes should be. Typical goals of sex therapy for many women with vulvodynia include managing expectations, identifying methods to reduce pain and increase enjoyment, improving communication, resolving conflicts and resentments that have built up over time and helping women change their attitudes towards themselves as sexual beings.

Sex therapy is more directive than regular psychotherapy, meaning that therapists often guide women (and their partners) into discussions of specific issues, including current sexual activity, physical and emotional responses to sex and sexual fears, among others. Homework assignments may also be given. If something feels too difficult or "not right," a woman should communicate this to her therapist. The more honest a woman is, the more helpful her therapist can be.

Therapy Approaches

Sex therapists utilize an array of treatment modalities and approaches. A few examples include mindfulness, sensate focus and continuing education. Mindfulness can help a woman focus on the pres-

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NVA Awards New Research Grants

Our donors' generosity has enabled the NVA to award nearly \$1 million in research grants since the creation of our Medical Research Fund. Many of our grant recipients have been successful in using preliminary data collected with NVA funds to secure large multi-year grants from the National Institutes of Health (and other institutions) to continue their research. The studies summarized below were among many excellent proposals submitted during our first 2012 grant cycle, and were recently approved for funding by the NVA's Board. Applications submitted during the second cycle are currently being reviewed by an expert panel, and recipients will be announced in early 2013. Previously funded projects, and their published results, are summarized on our website: www.nva.org/research_fund.html.

Andrea Rapkin, MD & Emeran Mayer, MD
UCLA Dept. of Obstetrics and Gynecology & Center for Neurovisceral Sciences and Women's Health



Efforts to identify effective treatment for vulvodynia have been hampered by our limited understanding of the condition's causes and underlying mechanisms. To remedy this situation, Rapkin and Mayer will use their NVA grant, *An MRI Study to Investigate Differences in the Brain's Structure and*

Function, which was matched with an impressive amount of funding from UCLA, to identify novel biological markers, i.e., "biomarkers," of two vulvodynia subtypes: Generalized Vulvodynia and Provoked Vestibulodynia. Women will undergo functional resting state MRI to evaluate patterns of structure and activity in the brain at rest, as well as structural MRI to obtain various measures of the brain's grey matter (e.g., cortical thickness, volume, shape). Because Dr. Mayer participates in the \$40 million NIH-funded *Multidisciplinary Approach to the Study of Chronic Pelvic Pain* (MAPP) Network, an added benefit of this study is that imaging data from women with



vulvodynia will be compared to data from hundreds of women with irritable bowel syndrome, interstitial cystitis/painful bladder syndrome and controls collected through the MAPP study. The data will be used to determine whether symptom-based pain syndromes share certain characteristics, as well as identify vulvodynia subtypes associated with specific biomarkers. Further, they will correlate findings of brain scans with known genetic and early environmental risk factors for chronic pain. The long-term goal of this study is to identify biomarkers for different vulvodynia subtypes that can serve as novel treatment targets, and to use this information in developing large controlled trials to test the effectiveness of various treatments for vulvodynia.

Alice Rickard, MS
St. Louis University Dept. of Pathology

The epithelium covers the exterior surfaces of the body, lines the closed internal cavities and forms the secretory glands. The epithelium can provide an impervious barrier, as in the bladder, and can also form a continuous cellular layer that separates the underlying connective tissue from the external environment, as in the vulva.



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NVA Helps to Establish New Clinics

The *Dr. Stanley C. Marinoff Vulvodynia Career Development Award* has played an instrumental role in expanding the field of clinicians and researchers working to advance clinical care and scientific understanding of vulvodynia. The NVA's Board recently selected the 2012 Marinoff Career Award recipients, both of whom will use NVA funding to develop vulvar pain clinics within their respective institutions. To read summaries of prior awards, and their outcomes, please visit www.nva.org/career_development_award.html.

Jennifer Greene, MD

University of South Carolina School of Medicine



Dr. Greene will use her award, generously matched by her institution, to establish the first vulvar specialty clinic at her university, which serves as a referral center for the Columbia metropolitan area and 17 surrounding counties. Her goals are to better serve the medical needs of women

with vulvar disorders in the community and to train the next generation of gynecologists, including medical students and residents. Dr. Greene will also conduct clinical research in her patient population to better understand vulvodynia treatment outcomes. For more information on the clinic, which opened in August, call 803-545-5700 or visit www.med.sc.edu/news.7.25.12.asp.

Ewa Baszak-Radomska, MD, PhD

TERPA Offices, Poland



Dr. Baszak-Radomska will establish the first dedicated vulvar pain clinic in Poland. Specifically, the NVA's funding will assist the clinic staff in serving low-income patients, as well as providing multidisciplinary medical care to women suffering from vulvodynia and related

pelvic pain disorders. Dr. Baszak-Radomska is also the founder of the Women Without Pain Foundation, whose mission is to raise awareness of neglected pain disorders, educate and train medical professionals and improve medical care provided to women suffering from these conditions in Poland. For additional information, please visit www.terpa.eu/ and <http://kobietabezbolu.pl/>. ■

NVA Awards

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Whereas the bladder epithelium has been widely researched, only one study on vulvar epithelial tissue has been conducted to date. In order to understand the underlying mechanisms of vulvodynia, it's essential to obtain this basic information on the make-up of vulvar tissue. With her NVA grant,

Characterizing Vulvar Epithelial Tissue in Women with Vulvodynia, Rickard will study the composition of vulvar epithelial tissue taken from women with vulvodynia and compare it to control tissue, as well as bladder epithelium from women with interstitial cystitis. Results will determine whether vulvar epithelium is defective in women with vulvodynia, identifying a new avenue for therapeutic intervention. ■

In Memory and Appreciation of Nancy Westman



The NVA is saddened by the loss of a wonderful caring friend, dedicated advocate and generous contributor. Surrounded by those who were most dear to her, Nancy Westman, age 81, passed away peacefully on August 31, 2012, in her Madison, Wisconsin, home.

We have been deeply moved by the generosity of Nancy's family members and friends who have honored her memory by donating to this cause to which she was so committed. Nancy specifically wanted her request for memorial donations to be used to bring attention to this common problem that is not commonly known. She carried a cushion with her for comfort wherever she went, and used it as a segue to discuss vulvodynia with

those who were unfamiliar with it.

Nancy wanted to do all she could to help other women with the disorder, and was active in the Madison-area NVA support group since it began in the mid-'90s. Despite her physical challenges, Nancy was always upbeat and ready to brighten your day with the most contagious smile. Her interest in other people and devotion to worthwhile causes helped to divert her attention from her own discomfort. In addition to her longstanding generous commitment to supporting the NVA's mission, Nancy routinely took the time to send touching notes of encouragement and support, which we will always treasure dearly.

We extend our heartfelt condolences to her husband, Dr. Jack Westman, and to their three sons, Daniel (Alison), John (Jan), and Eric (Gretchen), and nine grandchildren, Matthew, Laura, Carly, Peter, Megan, Eric, Luke, Clay, and Alexander. ■

Sex Therapy

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ent moment and decrease anxiety related to thinking about the past and the future. This redirects the woman from such distracting thoughts and enables her to better focus on appreciating physical sensations in the present moment. Sensate focus, a series of exercises that helps a woman get back in touch with her senses, is often a part of treatment. It's designed to decrease a woman's anxiety and pressure and increase relaxation, comfort and emotional connection with her partner. Sensate focus is not directed toward a specific goal such as intercourse or orgasm, and usually involves temporarily suspending intercourse. Sex therapy also

involves continuing education. Learning more about sexual anatomy and physiology, through discussion and reading assignments, helps to separate sexual myths from reality and give couples new insight.

Collaborative Care

Effective sex therapy usually includes referral to, and evaluation by, other professionals who can, as a team, help to support women through the process. Sex therapists should have colleagues to whom they routinely refer patients to rule out or treat other conditions that may be causing sexual pain or limiting sexual activity. This includes

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Sex Therapy

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experts in gynecology, physical therapy, neurology/anesthesiology, psychiatry and psychopharmacology, among others. Ongoing collaboration between the sex therapist and other professionals treating/supporting a woman as she undergoes sex therapy can be invaluable.

Getting Started

No matter where a woman with vulvodynia is in her lifecycle, sex therapy can be helpful. A word to the wise about timing – many couples wait until they want to conceive to start therapy. It's best for couples to allow for sufficient time for therapy to help them develop a more satisfying sexual relationship before taking on the challenges of preg-

nancy, childbirth and caring for an infant. It's important for a woman to remember that consulting a sex therapist does not mean she has a bad relationship – it's something that couples who have loving relationships do to deal with specific problems and bring more happiness to their lives. Sex therapy can sometimes prove to be more challenging than a woman expects. It takes courage to address vulvodynia's impact, but many women and couples who've gone to therapy experience more satisfying sex lives and relationships. Taking care of ourselves and our relationships is an investment worth making. If sexual pain is an issue for you, there's no time like the present to seek the help you need. ■

NIH Investment

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study will significantly impact our scientific understanding of risk factors and mechanisms underlying these conditions that frequently co-occur.

Peter Smith, PhD

*University of Kansas Medical Center
Institute for Neurological Disorders*

Prior studies demonstrate that women with PVD have an increased number of pain-sensing nerve fibers in the vestibule, termed "hyperinnervation." Clinical evidence also suggests that reproductive hormones, such as estrogen



and progesterone, influence the development and severity of the condition. Smith has developed an animal model of PVD that replicates many clinical findings in women, and in his current study, *Identifying Therapeutic Targets for Vulvodynia*, will use it to assess potential biological mechanisms to target with current/novel therapies. His research team will investigate the persistence of hyperinnervation, and its correlation to vestibular sensitivity, in their rat model of PVD. Then they will assess how estrogen and progesterone affect the development of hyperinnervation, and compare animal tissue to vestibular tissue from women with PVD. Smith will test the theory that activating a specific cell receptor (angiotensin II receptor type 2) decreases hyperinnervation and hypersensitivity. Based on the hypothesis that inflammatory cells create a hormone, angiotensin II, that initiates sensory nerve sprouting, Smith will investigate whether blocking angiotensin II receptors not only prevents, but reverses,

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In Her Own Words

Dear NVA,

In fall 2010 I was told that I had vulvodynia. I finally saw a specialist about a year later who diagnosed me with Provoked Vestibulodynia and recommended surgery. She also recommended that I join the NVA. The NVA connected me with a support group and various resources that helped me to prepare for my surgery. I went into the procedure completely confident that this was the right treatment path for my condition. My surgery was extremely successful and I am now completely pain-free!

When planning our wedding, my fiancé and I wanted to do something in lieu of the traditional glass-clinking to get us to kiss during the reception. We knew another couple who took donations for an organization and cause that they cared about. After my surgery, I was reading an NVA newsletter and remembered how much pain I had been in, and how lucky I was to have such a successful treatment outcome. I tearfully asked my fiancé if our donations could be sent to the NVA. He agreed that the NVA had helped me so much and that we shouldn't forget that although I was out of pain, there are many women still suffering and that more research is needed.

Here is what we told our guests: "Instead of the traditional glass-clinking to get the bride and groom to kiss tonight, Martha and Justin have decided that in order for them to kiss, you will need to make a donation. You probably know that both Martha and Justin have had surgery in the past year, so they have seen first-hand how important donations to medical charities are. The organization that they will be donating to is the NVA, a medical charity that has helped them. Please donate as you are able. The more donations, the more you make them kiss!"

Enclosed are the donations that our guests contributed at our wedding reception.

Being pain-free has completely changed our lives, and I cannot thank the NVA enough for having the resources and information available when I needed them most.

Sincerely,

Martha Klasen Ranek & Justin Ranek



New Treatment Helpful in PVD Subgroup

Questions & Answers with Yaniv Farajun, MD, and Jacob Bornstein, MD, MPA

Dr. Farajun, who recently completed his residency training in obstetrics and gynecology at Western Galilee Hospital in Nahariya, Israel, is the 2009 recipient of the Dr. Stanley C. Marinoff Vulvodynia Career Development Award. He used his NVA award to conduct a research study with Dr. Bornstein, chair of the department of obstetrics and gynecology at Western Galilee Hospital, and president of the International Society for the Study of Vulvovaginal Disease. The doctors recently published the study's findings, which are summarized in this interview, in the medical journal Obstetrics and Gynecology.

NVA: What have your prior studies shown?

Drs. Farajun & Bornstein: We've published the outcome of several studies that compared vestibular tissue from women with Provoked Vestibulodynia (PVD) to that of controls. We found that PVD tissue contained an increased number of mast cells – connective tissue cells that release histamine and other mediators in response to injury or inflammation into the surrounding tissue. Further, we discovered elevated numbers of pain-sensing nerve fibers and increased activity of heparanase, an enzyme that degrades heparan sulfate in the extracellular matrix of many tissues (Bornstein 2008, Bornstein 2004).

NVA: How do these findings relate to the hypersensitivity that women experience?

Drs. Farajun & Bornstein: Heparanase may degrade vestibular tissue, thus allowing the nerve endings to penetrate through a part of the vestibular tissue. Also, the release of nerve growth factor from mast cells may cause pain-sensing nerve fibers to increase in number or “proliferate.” We hypothesized that the combination of these factors is likely the cause of vestibular hypersensitivity experienced by women with PVD.

NVA: What were the goals of your study?

Drs. Farajun & Bornstein: Very few placebo-controlled studies have investigated the effectiveness of PVD treatments. Our goal is to translate our tissue discovery into meaningful results for the patients that we care for. Logically, the next

step was for us to identify a treatment that counteracts what we found in our tissue studies and determine whether it helps to decrease vestibular pain in women with PVD.

NVA: What treatment did you select? Why?

Drs. Farajun & Bornstein: For our trial, we chose enoxaparin, a low-molecular weight heparin, because it has been shown to inhibit heparanase activity.

NVA: How was the study conducted?

Drs. Farajun & Bornstein: Forty (40) reproductive-aged women who had severe PVD participated in our randomized, double-blind, placebo-controlled trial. After meeting all inclusion criteria and undergoing a thorough medical examination, participants were randomly and blindly assigned to two groups to receive either enoxaparin or placebo. We biopsied the most painful vestibular sites and evaluated the tissue to determine the number of mast cells, amount and localization of nerve fibers and heparanase activity. Women self-administered daily subcutaneous abdominal injections of either 40mg enoxaparin or 40mg saline placebo for 90 days. Because possible side effects of enoxaparin, an anti-coagulant, include bruising and abnormal bleeding, women underwent blood tests, kept a log book and immediately notified study personnel of any side effects.

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New Treatment

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NVA: How did you evaluate the treatment's effectiveness?

Drs. Farajun & Bornstein: We evaluated women's pain scores and vestibular sensitivity by administering a cotton-swab test prior to starting treatment, at the end of the treatment phase and again three months later. Women completed several validated questionnaires, including the Brief Pain Inventory, short form McGill Pain Questionnaire and the International Society for the Study of Vulvovaginal Disease Vulvodynia Questionnaire, several times throughout the study's duration. We also took a second vestibular biopsy (parallel to the first biopsy site) at the end of the study and analyzed the number of nerve fibers, mast cells and heparanase activity in the vestibular tissue.

NVA: How well did women comply with treatment?

Drs. Farajun & Bornstein: Women in the treatment group administered 98 percent of their injections and women in the placebo group administered 96 percent of their injections. This difference was not statistically different. The high compliance rate is likely due to the fact that women who participated in our study had failed more conventional therapy (e.g., physical therapy, topical creams), and the injections were their last option before resorting to surgical removal of the painful tissue.

NVA: What did you find?

Drs. Farajun & Bornstein: Overall, women treated with enoxaparin showed a significantly greater reduction in vestibular sensitivity at the end of treatment (and three months later) compared to the placebo-treated group (29.6% vs. 11.2%). Seventy-five (75) percent of the treatment group reported more than a 20 percent pain reduction, compared with 28 percent of the placebo group. Seven enoxaparin-treated women (compared with

three in the placebo group) had almost painless intercourse at the end of the study. Altogether, 47 percent of the enoxaparin group, compared with only 25 percent of the placebo group, reported improvement in pain during intercourse. When analyzing the questionnaire data, although not statistically significant, we found that women in the enoxaparin group reported a greater percentage of pain reduction compared with the placebo group during intercourse (28.9% vs. 4.4%), tampon insertion (31.1% vs. 0%), and voiding after intercourse (52.2% vs. 32.4%). In women who reported improvement of sensitivity at the vestibular site parallel to the original biopsy site, we found a reduction in the number of pain-sensing nerve fibers in the enoxaparin group. Interestingly, in women who reported improvement in symptoms at the end of the trial, mast cell counts and heparanase activity were slightly lower in the enoxaparin-treated group compared to those who received placebo injections.

NVA: What conclusions can you draw from these findings?

Drs. Farajun & Bornstein: Due to a lack of prior research, very few studies have investigated vulvodynia treatments in a randomized controlled trial, so the significant pain reduction reported by a subgroup of participants with enoxaparin treatment is of clinical importance. Additionally, we were able to correlate pain reduction with a decrease in the number of nerve fibers in vestibular tissue obtained from women in the enoxaparin group, but not in the placebo group. This finding also validates the theory previously discussed – that the increased pain sensitivity experienced by women with PVD is likely related to the number of pain-sensing nerve fibers in the tissue. Through this study, we've discovered a new potential

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Guttmacher

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delineate priorities and develop a strategic plan that will guide the Institute's work throughout the next decade. One significant outcome will be the creation of the first dedicated gynecologic research branch in the NIH's history. Dr. Guttmacher is now beginning the implementation process, and we recently

sat down with him to discuss his vision for this new branch and the Institute as a whole.

NVA: What interested you in the position of NICHD Director?

Dr. Guttmacher: The NICHD's mission addresses several areas that I am passionate about. I very much enjoyed my prior position and work at the NIH's National Human Genome Research Institute, but I really missed my roots as a pediatrician and my longstanding interest in reproductive health. The issues that I care the most about happen to fall under NICHD's purview, so it was a wonderful opportunity and natural fit for me.

NVA: Could you briefly describe the "vision" process? Why did you feel this was necessary and important?

Dr. Guttmacher: As the new director, rather than dictating the Institute's future research priorities, I instead chose to bring together a diverse group of people – NIH researchers, investigators from institutions outside of the NIH, clinicians, public policy professionals, advocates – and take advantage of their wonderful knowledge, expertise and creativity to identify and capitalize on exciting research opportunities. This is particularly important to do with a leadership change. The vision process focused on our extramural program,

i.e., research that we fund at universities across the country, and we hope it sent a clear message to the scientific community, particularly during this time of fiscal uncertainty and flat budgets, that the NICHD is still very much committed to supporting new and ambitious medical research. We convened nine separate workshops on topics that span NICHD's diverse mission. I wanted to ensure that the resultant strategic plan would use taxpayer dollars – wisely and well – to advance cutting-edge research pertaining to our mission.

An unanticipated benefit of the vision process was that I was able to get to know a diverse group of medical, scientific and policy professionals who work outside of the NIH, but are interested in and



NICHD Mission

The mission of the NICHD is to ensure that every person is born healthy and wanted, that women suffer no harmful effects from reproductive processes, and that all children have the chance to achieve their full potential for healthy and productive lives, free from disease or disability, and to ensure the health, productivity, independence, and well-being of all people through optimal rehabilitation.

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already working toward advancing parts of the NICHD's mission. They were also able to get to know me better. The resulting collaborative relationships will enable us to translate NICHD-funded scientific discoveries more effectively and efficiently into meaningful change in the lives of those for whom the research was conducted to begin with.

NVA: What changes in the Institute's structure and function have resulted from the vision process?

Dr. Guttmacher: The NIH is increasingly asking scientists at academic institutions across the globe to break down the barriers that separate them and conduct research in an interdisciplinary fashion. If we at the NIH are asking the external medical-scientific community to do this, then I feel that our Institute needs to lead by example and do the same. As much as possible, I want to get rid of the barriers that have hampered collaboration among NICHD's numerous research branches and create an organizational structure that stimulates productivity and effectiveness.

Previously, the individual research branches were grouped together by topic under four "Centers," each with its own chief, who served under the NICHD director and deputy director. Going forward, we have eliminated all of the Centers but one, and research branch chiefs will serve under the director of extramural research, who will serve under our deputy director and myself. After a national search that attracted truly impressive applicants, we recently appointed Cathy Spong, MD, an obstetrician-gynecologist who for many years has headed NICHD's Pregnancy and Perinatology extramural branch, to this newly created position of director of extramural research. She will play a major role in implementing this reorganization. As part of the reorganization, we felt it was im-

perative to add two new branches – the Pediatric Trauma and Critical Illness Branch, and the Gynecologic Health and Disease Branch – to the 10 that were already in place.

NVA: Creating a new branch, in essence, means that you have voluntarily stepped up to hold the Institute accountable for major progress in this area. In this fiscally challenging time, why did you deem it imperative to do so specifically for gynecologic research?

Dr. Guttmacher: Even though NICHD has been supporting gynecologic research for quite some time, we recognized that we could be even more productive by centering this effort in a single branch devoted solely to gynecologic disorders. By applying new approaches and identifying promising research opportunities, we have a real opportunity to make major inroads in the coming years, thereby improving the health and well-being of millions of women and their families. We want to make sure that our structure is optimal to take advantage of this opportunity.

NVA: To begin, what conditions will this branch cover? How will it be staffed?

Dr. Guttmacher: Vulvodynia, chronic pelvic pain, endometriosis, pelvic floor disorders and uterine fibroids will be "housed" in this branch, and NICHD staff are currently in the process of thoroughly reviewing all NICHD-funded grants to identify other conditions that may be appropriate to include. It will have its own acting branch chief and other staff members to begin. We've waited a long time to establish this branch, so we want to make sure that we take the time to identify the right permanent leader with the appropriate background and expertise. I anticipate this person being in place in early 2013.

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Guttmacher

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NVA: What do you hope this branch will accomplish? How will you measure its progress and success?

Dr. Guttmacher: There are some indirect measures we can use to monitor progress, such as the number, quality and scores of vulvodynia research applications submitted over time. However, the NIH doesn't exist merely to fund research – we exist to make a real and meaningful impact in people's lives. If we can look back and clearly see that this branch not only catalyzed real scientific progress in this and other neglected areas, such that we have a better understanding of vulvodynia's causes, mechanisms and risk factors, but also see that these findings have been translated into meaningful change, such that women's health and quality of life have dramatically improved, I will consider the branch a success.

NVA: Is there anything else you'd like to share with our readers?

Dr. Guttmacher: One of the guiding tenets of both our scientific vision process and our structural reorganization is that collaboration is the key to advancing science and improving health. Thus, the vision process was maximized by involving not just NICHD staff, but folks from various parts of NIH, our research community and others interested in our mission. And the reorganization is designed to further collaboration among NICHD, other NIH Institutes, and many (previously separate) entities of the research and public communities. To solve the pressing scientific and health needs of the future, we will need to continue to develop innovative ways to bring to the scientific process diverse "stakeholders" with interests in NICHD's wonderful mission. ■

Nerve Blocks

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mood, so that we could design a large clinical trial targeting women who were most likely to respond favorably to the treatment.

In our NVA-funded study, we enrolled 32 women with GVD aged 18 to 65 who had previously failed to benefit from medical therapy. In order to participate, women had to report unprovoked vulvar pain that was not limited to the vestibule for at least six months. The majority (88%) of our study population experienced concurrent vestibular pain. Some in the medical-scientific community have proposed that pudendal neuropathy or pudendal nerve entrapment (PN/PNE) may be the cause of generalized vulvar pain in many women (Labat 2008). We did not exclude women with evidence of PN/PNE based on Nantes crite-

ria: burning, shooting, stabbing pain or allodynia (pain in response to a non-painful stimulus such as pressure from a cotton-swab) in the anatomical territory of the pudendal nerve that is worsened by sitting, does not wake the patient at night, is without objective sensory loss on clinical exam, and is alleviated by a pudendal nerve block (Labat 2008). Many individuals with supposed PN/PNE who meet Nantes criteria will have longstanding relief with local anesthetic nerve blocks (Robert 2005). We were not able to determine if any of the women who participated in our study had PN/PNE, as it is a diagnosis that can only be confirmed after a positive response to pudendal neurolysis, i.e., destroying the nerve (Hibner 2012).

The mean age of our study population was 44. On average, women had symptoms for four years.

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Only five percent were not sexually active, and all but two reported pain during/after sex. Nearly half were postmenopausal, 40 percent of whom were using hormonal contraceptives. Approximately 56 percent of the women were currently using medications for pain management, including tricyclic antidepressants, anticonvulsants, benzodiazepines, serotonin norepinephrine reuptake inhibitors, lidocaine and narcotics. Most had used at least two different classes of medications in the past, including antidepressants (75%), anticonvulsants (43%), local anesthetics (28%) and narcotics (34%). Additional prior therapies included physical therapy (56%), psychological therapy (21%), acupuncture or transcutaneous electrical nerve stimulation (40%), meditation or yoga (34%) and homeopathy (18%). Three women failed trials of implantable spinal cord stimulators. Forty-six (46) percent of women reported at least one concurrent pain diagnosis including: migraine headache (15%), endometriosis (12%), fibromyalgia (12%), irritable bowel syndrome (28%), temporomandibular disorders (6%), bladder pain syndrome/interstitial cystitis (15%), low back pain (12%) and abdominal pain or gastroesophageal reflux disease (6%).

The study protocol involved a telephone screen and six sessions – five local anesthetic nerve block sessions performed every two weeks, and a post-treatment visit (or email contact) eight to 12 weeks later. Women who met the inclusion criteria after the history and physical exam were asked to complete a series of questionnaires, including the UCLA Pelvic Pain Questionnaire, McGill Pain Questionnaire, Female Sexual Function Inventory (FSFI), Beck Depression Inventory (BDI), Hospital Anxiety and Depression Assessment and the Early Trauma Inventory Self-Report Short Form. Women completed the McGill Pain Questionnaire at the beginning of each session and the McGill, BDI and FSFI at the post-treatment visit. Because

women with GVD often have pain that moves to different areas of the vulva from day-to-day and may not experience allodynia (i.e., pain in response to a non-painful stimulus such as pressure from a cotton-swab), we did not use a vulvalgesiometer to assess vulvar pain severity.

We performed local anesthetic nerve blocks in the following order. We first administered the caudal epidural block using 10 ml of 0.2% ropivacaine through the sacral coccygeal hiatus (see diagram on p. 18). Next, we performed transvaginal pudendal nerve blocks using 5 ml of 0.25% bupivacaine bilaterally, through an Iowa Trumpet (see diagram on p. 19). Finally, we performed a transperineal vulvar infiltration using 10 ml of 0.25% bupivacaine at the 6 o'clock position below the vestibule while directing the 22-gauge, 1.5-inch needle to the right and left of the vestibule. There were no complications such as significant post-injection pain, hematoma or infection, although one woman experienced a prolonged inability to void and required a Foley catheter for two days.

We found that women's pain significantly decreased between the first and last visits. Forty-three (43) percent of women were "responders," which we defined as achieving a 50 percent decrease in their score on the McGill Pain Questionnaire. Depression also significantly improved between the first and sixth visits. Unfortunately, in contrast to what we found in our prior study of women with PVD, women with GVD did not report significant improvement in sexual desire, arousal, lubrication, orgasm, satisfaction or sexual pain score between the first and last visits. The only variable found to either negatively or positively predict treatment response was pain severity during the first visit. Women whose pain was more severe at baseline

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were significantly less likely to improve with the block series. Pain duration, depression, history of trauma and number of concurrent pain diagnoses failed to predict treatment response.

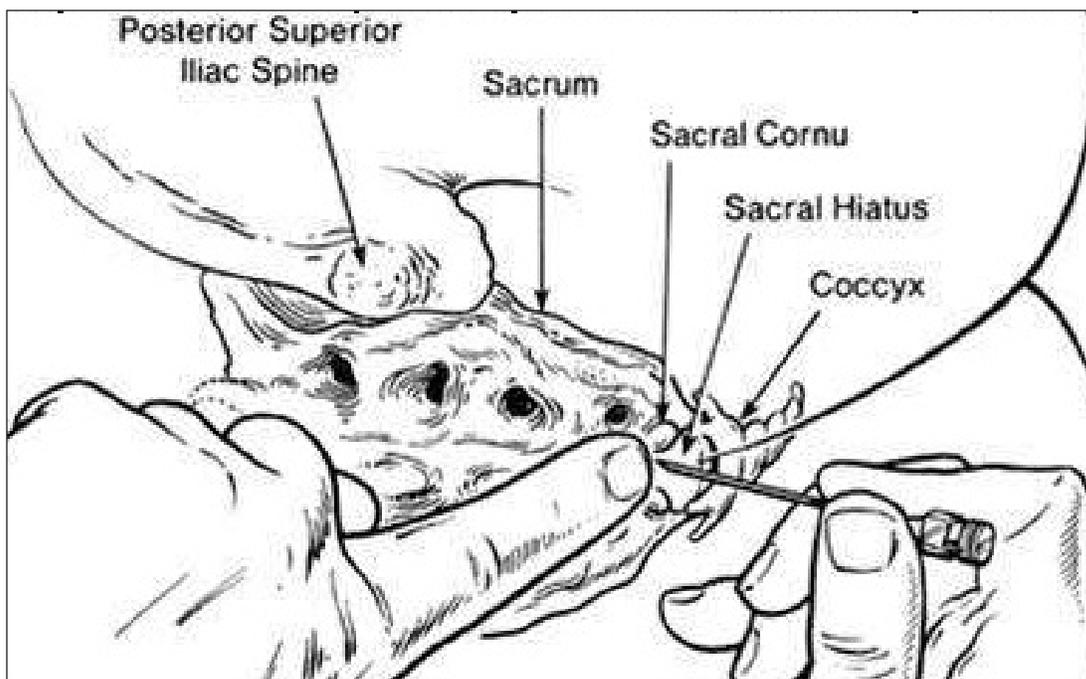
This pilot study is limited by its failure to include placebo injections. An uncontrolled trial cannot preclude a placebo response, even if the participants, as in the current study, had failed to respond to prior treatments. Although an uncontrolled study fails to provide a scientific basis for a therapeutic intervention, it was important to conduct this pilot study to obtain preliminary data on the treatment's effectiveness in women with GVD and to begin to identify factors that may predict treatment success or failure.

In conclusion, our series of five local anesthetic nerve blocks resulted in a modest treatment response. Although depression improved, sexual functioning did not, suggesting that more com-

prehensive multidisciplinary treatment may be needed to help women restore sexual function (see article on sex therapy, p. 5). More severe pain at baseline was associated with less pain relief. In clinical practice, many women with vulvodynia, similar to those with other pain disorders, benefit from a multidisciplinary approach, including physical therapy, pharmacotherapy and psychological approaches to reduce stress, depression and anxiety (Bergeron 2001). Further studies of those who experience long-standing relief from nerve blocks may help to determine the characteristics of women with GVD who are most likely to respond to this approach, as well as the role of nerve blocks in multidisciplinary pain management.

[Editor's Note: The results of Dr. Rapkin's studies investigating the effectiveness of this block series

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Source: www.pitt.edu/~regional/Caudal/caudal_block.htm

Nerve Blocks

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in women with PVD and GVD are reported in full in: Rapkin AJ, McDonald J, Morgan M. Multilevel local anesthetic nerve blockade for the treatment of vulvar vestibulitis syndrome. *Am J Obstet Gynecol.* 2008;198:41.e1-41.e5; and McDonald JS, Rapkin AJ. Multilevel local anesthetic nerve blockade for the treatment of generalized vulvodynia: a pilot study. *J Sex Med.* 2012 Aug 27. doi: 10.1111/j.1743-6109.2012.02909.x. (Epub ahead of print).]

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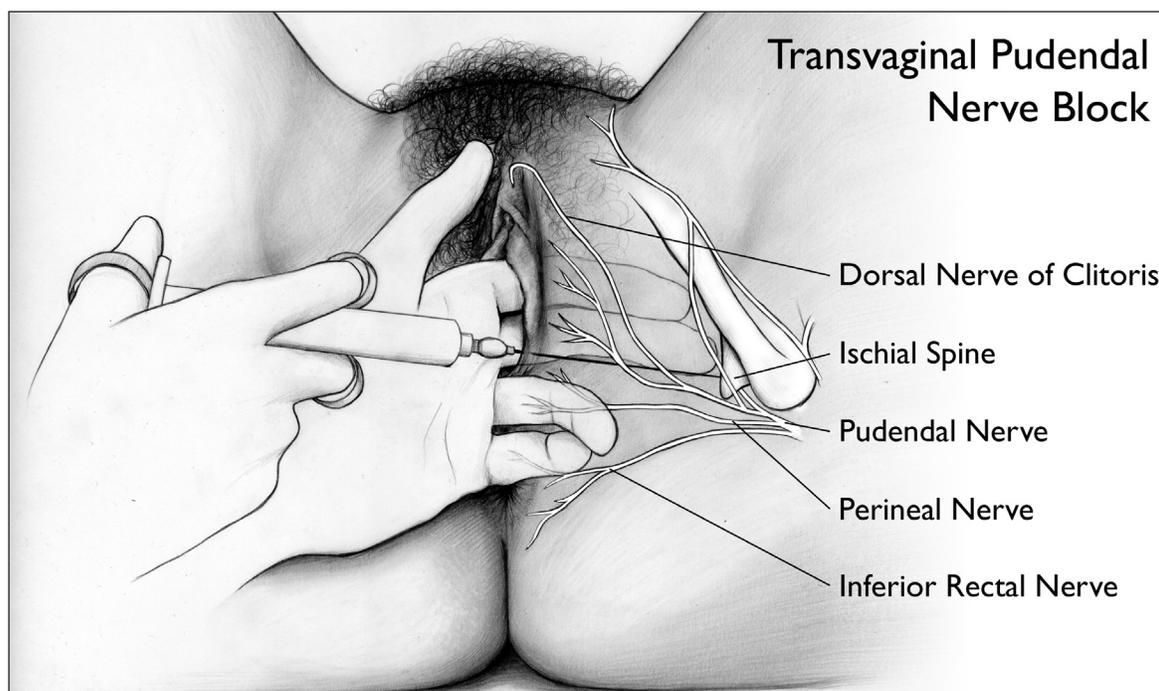


Diagram courtesy of Dawn Danby & Paul Waggoner

New Treatment

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treatment for this pain disorder – either alone or in combination with other treatments. Although the treatment response rate was not overwhelming for all women, it does appear to work for a subgroup of patients, to whom the treatment is extremely valuable. The next step is to try to identify predictors of treatment success that can be utilized in clinical care.

NVA: How can we use these findings to improve clinical care for women with vulvodynia?

Drs. Farajun & Bornstein: In order to improve clinical care for women with vulvodynia, we need to not only study the effectiveness of treatments for the condition in a randomized, controlled and blinded fashion, but to identify clinical characteristics that predict treatment response. Although the injections reduced pain in a subgroup of women with severe longstanding symptoms, based on our findings, a specific subgroup of women with PVD, i.e., women in early stages of the disorder, may benefit the most because enoxaparin could hinder the proliferation of nerve fibers and subsequent progression to chronic irreversible pain. Future studies utilizing different daily doses and longer time periods are warranted, as are studies that identify predictors of treatment failure/success that can be incorporated into the clinical care of women with this life-altering pain condition.

[Editor's Note: The results of Dr. Farajun's study are reported in full in: Farajun Y, Zarfati D, Abramov L, Livoff A, Bornstein J. Enoxaparin treatment for vulvodynia: A randomized controlled trial. Obstet Gynecol. 2012;120:565-72.]

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NIH Investment

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hyperinnervation and hypersensitivity. This research will provide fundamental information on mechanisms that regulate nerve supply in normal and inflamed vestibular tissue, which may substantively change the medical management of certain vulvodynia subtypes. ■

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