National Vulvodynia Association

NVA News

Volume XVIII, Issue II Winter 2014

Pharmacological Management of Vulvodynia

Questions and Answers with Justin Wasserman, MD

Dr. Justin Wasserman is a board certified physical medicine and rehabilitation specialist with expertise in the pharmacological management of chronic pain disorders, including vulvodynia. His private practice is located in Bethesda, Maryland.

NVA: What does research suggest are the causes or triggers of vulvodynia?

Dr. Wasserman: Although we don't yet fully understand vulvodynia's causes, research suggests that there are many different triggers that lead to the development of, and mechanisms that underlie, vulvodynia symptoms. For instance, some women may have a genetic predisposition to developing "centralized pain" in different areas of their bodies. This type of pain is primarily driven by some form of pathology or dysregulation within the central nervous system (CNS, i.e., brain and spinal cord) where the brain abnormally amplifies, or even initiates, abnormal pain signals. Fibromyalgia is one example, wherein the sufferer perceives diffuse body pain even though there is no actual orthopedic trauma or injury. In the case of vulvodynia, many different triggers or initiating events have been reported and studied, such as repetitive vaginal fungal or bacterial infections and an abnormal immune system response to vulvar irritation. Regardless of the initial trigger, a cascade of changes in the CNS results and continues long after that triggering event is treated or subsides, thereby leading to the development of a chronic vulvar pain state.

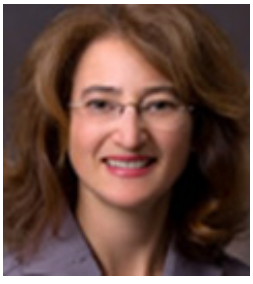
NVA: What are some recent vulvodynia research advances? What do you anticipate in the future?

See PHARMACOLOGICAL, page 7

Vestibular Tissue Changes in Women with PVD

Results of First NVA-Funded Study of Menopausal Women

By Catherine Leclair, MD, Martha Goetsch, MD, MPH, and Terry Morgan, MD, PhD



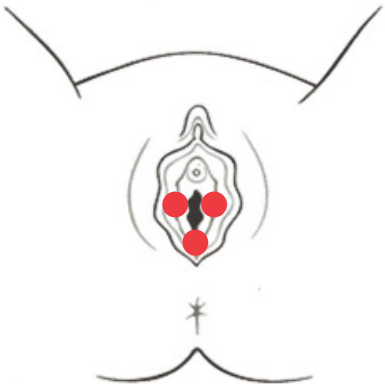
Dr. Leclair (pictured left) is an associate professor of obstetrics and gynecology at Oregon Health & Science University (OHSU) in Portland, where she directs the OHSU Program in Vulvar Health. Dr. Goetsch is an assistant professor of obstetrics and gynecology and has been actively engaged in the treatment and research of vulvodynia since the 1990s. Dr. Morgan is an associate professor, with appointments in the departments of pathology and obstetrics and gynecology. Drs. Goetsch and Morgan, also at OHSU, are pictured on page 13.

See TISSUE CHANGES, page 11

Definitions and Types of Vulvodynia

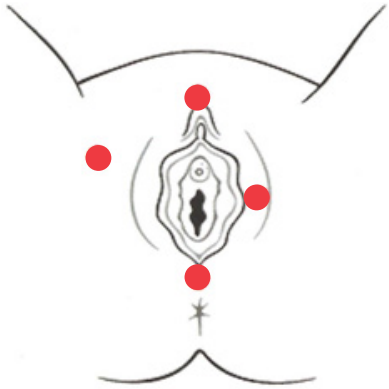
Many different terms have been used to describe vulvodynia. As a result, confusion among patients and medical professionals is common. To encourage consensus and clarify terms used in this newsletter, we have provided a brief summary of the most current definitions and classification. For more information,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

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
National Vulvodynia Association
P.O. Box 4491, Silver Spring, Md. 20914-4491
(301) 299-0775 ■ (301) 299-3999 (fax)
www.nva.org

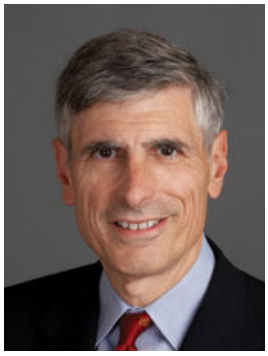
NVA News is published three times per year.

Phyllis Mate and Christin Veasley (Editors)
Andrea Hall (Layout)
Anne Modest (Contributor)
Cristina Shea (Contributor)

Lesson in Pain Relief - A Personal Postgraduate Experience

By Philip A. Pizzo, MD

Dr. Pizzo is the David and Susan Heckerman professor of pediatrics and of microbiology and immunology at Stanford University School of Medicine, and served as the Dean of the School of Medicine from 2001-2012. He was selected by the prestigious Institute of Medicine to chair our country's first study on the societal and economic impact of pain, which resulted in the landmark 2011 report, Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education and Research*. The following commentary was recently published in* The New England Journal of Medicine *(2013 Sep 19;369(12):1092-3), and has been reprinted with permission from the publisher*.



When I chaired an Institute of Medicine (IOM) committee on "Relieving Pain in America" and then co-authored a *Perspective* article about the vast human toll and financial burden imposed by chronic pain, I believed I understood the impact of chronic pain (1, 2). Not only did I have experience caring for children with life-threatening and frequently painful disorders, I also had relatives with chronic pain syndromes and had witnessed the limitations of the medical care system. But it wasn't until my own year-long journey with chronic pain that I received a higher level education on the topic.

I was loading a suitcase onto an airport conveyor belt, when an unexpected twist led to my first twinge of back pain. I assumed it would be self-limited, especially since I was in good physical shape: for the past several decades, I'd been running one to three marathons a year and working at demanding jobs, most recently as a medical school dean. I felt impervious to stress and was almost always optimistic. Chronic pain changed all that.

Two weeks later, I had another sudden onset of lower back pain and spasm. Unlike anything I'd ever experienced, it soon became localized to the left mid-buttock area. At that point, I sought medical guidance. In the year that followed, I became immersed in trying to assess the widely varying skills, strengths, biases, and deficits of various specialists and care providers. Complicating this variation was the limited evidence base regarding back and musculoskeletal pain. I was surprised by how quickly providers leapt to a default diagnosis that lay within their own comfort zone, even before gathering all the facts or performing a physical examination. Disk herniation was first on everyone's list — understandably, given its prevalence. When, after nearly 5 months, interventions including twice-daily physical therapy, acupuncture, deep tissue massage, and efforts to improve my posture had not alleviated my pain, I seemed to be moving out of the self-limiting clinical course generally associated with disk problems.

The patients with chronic pain who prove most challenging to clinicians are those whose physical evaluation, imaging, and other studies are negative or unrevealing. I was one of those patients. Despite symptoms that became more constant and incapacitating, two spine MRIs (6 months apart), an MRI of the pelvis, and one of the hip failed

See LESSON, page 4

Lesson

(from page 3)

to reveal a clear source. The pain migrated from the lateral buttock to the left ischial tuberosity and was not relieved by sitting, standing, walking, or lying down. One examiner noted a substantial loss of left hamstring strength. After 7 months, I began having radiating pain in the left leg, albeit not below the knee. As time went on and my symptoms and limitations worsened, various clinicians offered suggestions, which often differed from each other. Some clinicians wondered whether the pain was becoming "functional" (pain with no organic cause). Others strongly believed that it was probably neuropathic in origin, but without a defined trigger or site to explain it or to treat. I began having symptoms of clinical depression that contrasted starkly with my usual personality.

After 10 months of unremitting pain, many negative exams, and several ineffective injections of steroids and anesthetics into putative sites of nerve entrapment, efforts were made to refine the diagnostic assessment of the sciatic nerve, from its exit from the spine down to the leg. This was not a standard examination, but had it not been performed, the likely origin of my pain might still be undetermined. It proved diagnostic in defining a high branch of the left sciatic nerve that went through the body of the piriformis muscle. This branch innervated the hamstring muscle and helped to explain why a third of its strength had been lost. This finding was further verified by EMG and nerve-conduction studies. Presumably, it was a congenital aberration with which I had lived successfully for more than six decades. Although there is much debate about the "piriformis syndrome," in my case the sciatic entrapment was now well defined. The cascade of events following my initial injury was probably exacerbated by the stretching and pelvic anteversion efforts made to improve my posture — an unintended consequence.

The diagnosis was further confirmed by surgery, which appears to have been successful. Though it was a fairly major procedure, the relief from nerve entrapment and neuropathic pain was noticeable within days. Unfortunately, I proved highly sensitive to opiates and had two episodes of respiratory depression within days after surgery that required naloxone reversal and intensive care — a response that was not readily predictable and that underscores one of the dangers of using opiates for pain control.

While working with the IOM committee on pain relief, I learned a great deal about the facts, figures, and impact of chronic pain in the United States. But over the past year, I've learned new and very personal lessons about how chronic pain can negatively transform one's life force.

Previously, I had sometimes wondered whether the chronic pain that patients reported was as incapacitating as they claimed. I now know that it can become debilitating. It can take over one's life, sap one's energy, and negate or neutralize joy and well-being.

See LESSON, page 5

Lesson

(from page 4)

Although the question of whether depression antedates or is secondary to chronic pain is still debated, I learned that the sense of loss and the uncertainty that accompanies it can trigger manifestations of clinical depression that also require medical attention. These symptoms can rapidly reverse when the pain is relieved.

I learned that the experience of pain is highly individual, and that ways of measuring it, defining its triggers or causes, and addressing it are limited and subjective. Even sophisticated diagnostic studies lack the sensitivity to delineate subtle anatomical or physiological aberrations. I was fortunate to have an imaging study that defined the cause of my pain, but it is not one that's generally offered, and I could easily have been one of those patients who is told that a cause cannot be defined, nor a solution delineated.

I am confident that the various physician specialists I encountered were eager to help me, but many spent surprisingly little time and diligence thinking beyond the boundaries of their fields of expertise. Fortunately, I had an exceptional primary care physician who was able to coordinate, process, and lead — but that is often not the case for patients with chronic pain.

My experience underscores how much additional knowledge is needed to better define the causes and manifestations of pain, to calibrate its intensity more objectively, and to treat it more successfully and safely. I had a hard time calibrating my own pain on the traditional 1-to-10 scale, especially in the immediate postoperative period but also more generally. That difficulty has implications for the way pain is treated. And although we are all cognizant of the deaths that occur with opioid use and abuse, my experience raises the question of how much we know about the pharmacogenomics of these drugs and how well they are being monitored in clinical settings.

The IOM report laid out recommendations covering pain as a public health challenge, the care of people with pain, and the education and research challenges. The committee affirmed that "addressing the nation's enormous burden of pain will require a cultural transformation in the way pain is understood, assessed, and treated." My experience with chronic pain as a physician and as a patient underscores this conclusion and brings greater urgency to the implementation of the IOM committee's recommendations for relieving pain in America.

References

1. Institute of Medicine. Relieving pain in America: a blueprint for transforming prevention, care, education, and research. June 29, 2011 (http://www.iom.edu/Reports/2011/Relieving-Pain-in-America-A-Blueprint-for-Transforming-Prevention-Care-Education-Research.aspx).
2. Pizzo PA, Clark NM. Alleviating suffering101 — pain relief in the United States. *N Engl J Med* 2012;366:197-9. ■

Would You Like to Share Your Story?

Do you have a personal story about coping with vulvar pain that might help other women? If you would like to share your story in *NVA News*, please contact Phyllis Mate at pmate@nva.org.

NIH Funds Two New Vulvodynia Grants

Profiling Vulvodynia Based on the Neurobiological and Behavioral Endophenotypes (2013-2018)

Investigators: Andrea Rapkin, MD, Professor of Obstetrics and Gynecology, UCLA, and Jennifer Labus, PhD, Adjunct Assistant Professor, Semel Institute for Neuroscience & Human Behavior, UCLA

The treatment of vulvodynia (VD) is hampered by a lack of knowledge regarding its neurobiological basis. Our proposed study is based on the general hypothesis that, similar to other persistent pain conditions, VD clinical phenotypes are composed of multiple biological characteristics and that meaningful subgroups can be identified. In the current proposal, we plan to extensively phenotype a large sample of VD patients using functional and structural brain imaging together with genetic, physiological, and biological parameters. We hypothesize that central mechanisms (including alterations in the processing/modulation of signals from the external genitalia) are important determinants of the clinical presentation, and that differences in these brain signatures may play a critical role in treatment responsiveness. Such phenotyping has considerable implications for future drug development. We propose to test this hypothesis via three specific aims. Aim 1 will characterize alterations in multimodal structural brain and connectivity indices in VD. We will compare resting state [RS] functional and structural brain imaging in VD patients versus 200 age-matched female healthy controls, 200 patients with irritable bowel syndrome and 100 patients with painful bladder syndrome. Aim 2 will characterize the connectivity indices in VD and identify the association between structural (grey and white matter) and RS alterations and clinical, behavioral and genetic parameters. This will be accomplished by associating structural and RS functional abnormalities identified in Aim 1 with relevant characteristics including: clinical symptoms (severity, disease duration, co-morbid pain or psychiatric diagnosis), behavioral measures (pressure pain thresholds), and biological factors (gene polymorphisms related to hypothalamic-pituitary-adrenal axis function, pain, and inflammatory, catecholamine, and serotonin signaling systems). Aim 3 will identify VD patient subgroups by applying advanced mathematical classification techniques to brain, biological, behavioral and clinical endophenotypes. We plan to combine imaging and other phenotyping data to identify distinct VD subgroups.

Mechanistic Distinctions in Female Chronic Pelvic Pain Subtypes (2013-2016)

Colleen Fitzgerald, MD, Associate Professor of Physical Medicine and Rehabilitation, Loyola University, Chicago

Chronic pain is a highly prevalent health condition and women comprise a majority of all chronic pain populations, particularly persistent pelvic pain. Female chronic pelvic pain (CPP) is a rapidly growing and costly health concern, and may reflect a number of underlying diagnoses, including endometriosis, interstitial cystitis, vulvodynia and pregnancy-related pelvic pain. The frequent comorbidities shared by these pain conditions have been attributed to the complex interplay of somatic (cutaneous and musculoskeletal), visceral, and viscero-visceral crosstalk that shapes peripheral pain transmission within the pelvic girdle. Unfortunately, many previous attempts to understand normal and pathological variants of pelvic pain have primarily focused on these types of pain in isolation rather than considering system interactions. Our long term goal is to determine the differences between pelvic pain mechanisms critical to the understanding, classification, and treatment of these pain conditions. An examination of subtypes that are dominated by prototypical somatic features compared to visceral features will be undertaken. The short term goal of

See GRANTS, page 15

Pharmacological

(from page 1)

Dr. Wasserman: Some of the more interesting research is that which has attempted to determine what triggers chronic vulvar pain. A particularly interesting study by Ventolini and colleagues found that in some women, an abnormal inflammatory reaction to the Candida fungus triggered changes in their vaginal flora. If this is further studied and proven in a large sample, then perhaps interventions that prevent such an inflammatory reaction from occurring could be developed to prevent vulvodynia altogether (1). Other research in the area of radiological imaging of various chronic pain states, using tools such as functional MRI and PET scanning, presented by Dr. Emeran Mayer at the American Pain Society meeting this year, showed pretty convincingly that visceral pain is associated with abnormal pain modulation in the prefrontal cortex of the brain (2).

In another recent study published in the *New England Journal of Medicine*, Wager and colleagues, with the use of functional MRI of the brain, were able to identify a unique "neurologic signature" associated with the application of painful heat in people without chronic pain (3). In the 2013 University of Michigan study, which was summarized in the summer 2013 issue of *NVA News*, Hampson and colleagues demonstrated the existence of central sensitization in vulvodynia patients using brain imaging (4). When non-painful pressure was applied to their thumbs – an area of the body far from the vulvar region – women experienced pain whereas controls felt normal sensation. Once again, this article adds to the growing body of evidence signifying that many chronic pain states, including vulvodynia, are either caused or perpetuated by CNS abnormalities. In my opinion, Hampson's article, and other similar data, has profound consequences for the treatment of vulvodynia in that it clearly shows that treatments must be focused not just on the peripheral anatomic region of pain, e.g., the vulva, but must also be directed towards modifying abnormalities in the CNS that perpetuate the pain. I have no doubt that, in the not so distant future, we will have a much better understanding of how pain is processed and perpetuated in the brain, perhaps even at the genetic level, such that we may be able to more selectively block abnormal pain in conditions like vulvodynia.

NVA: What commonalities do you see among your vulvodynia patients?
Dr. Wasserman: Many, but not all, of my patients also suffer from coexisting pain syndromes such as fibromyalgia and chronic headache. They may also have difficulty with sleep, depression and anxiety. For some, these conditions begin at the same time as their vulvodynia, and for others, vulvodynia precedes or follows their development.

NVA: What treatments have women typically tried prior to consulting you?
Dr. Wasserman: Patients typically run the gamut of standard gynecological treatments for their vulvar pain prior to being referred to me. These include various topical preparations containing steroids, estrogen, anesthetics or other active ingredients, pudendal nerve blocks, and even failed surgeries. For these reasons, patients referred to me are those with longstanding vulvodynia and for whom complex pain management is the best approach.

NVA: What classes of medications can be helpful in treating vulvodynia?

See PHARMACOLOGICAL, page 8

Pharmacological

(from page 7)

Dr. Wasserman: We now have multiple classes of medications that have demonstrated effectiveness for patients with various pain disorders, particularly neuropathic pain conditions. One needs to keep in mind that all of these medications, when used for vulvodynia, are being used off-label. This is because, currently, there are no FDA-approved medications specifically indicated for the treatment of vulvodynia. Nevertheless, that should not hinder clinicians from utilizing various safe medications for which sufficient data supporting their effectiveness in treating neuropathic (or other) pain exists. These include SNRI medications (e.g., duloxetine, milnacipran), tricyclic antidepressants (e.g., amitriptyline, nortriptyline), gabapentinoids (e.g., gabapentin, pregabalin), anticonvulsants that act on various nerve channels (e.g., levetiracetam, lamotragin, tomiramate), the cannabinoid class of medications (i.e., medications that act on the same receptors as marijuana), NMDA receptor blocking agents (e.g., dextromethorphan, memantine) and opioids. These are very complex medications that should only be prescribed by clinicians who have extensive knowledge of, and experience with, their proper usage, mechanisms of actions, side effect profiles and drug interaction profiles. Opioids are the last resort in the treatment of any type of chronic pain, including vulvodynia.

NVA: How do you determine which classes of medications to use for different vulvodynia subtypes?

Dr. Wassermann: There are many things that I take into consideration when using medications for women with vulvodynia, including the potential side effect profile of a medication, other coexisting conditions that she may have, such as additional pain syndromes, muscular dysfunction, depression and sleep issues. Whether a woman's pain is provoked only, such as with Provoked Vestibulodynia, or spontaneous, as in Generalized Unprovoked Vulvodynia, doesn't typically influence my decision, because as I mentioned, the patients who come to me have had longstanding unremitting pain. Any pain that goes unmitigated like this can "centralize," so the medication target – the brain – is the same in both. I also pay very careful attention to a patient's description of how the pain first manifested and perpetuated, as this can provide important information and clues. Just as an example, for some of my patients with vulvodynia who also have pelvic floor muscular dysfunction, I might lean more towards starting with medications that target muscle tightness and centralized pain, such as tizanidine or alpha-2 agonists. If a woman has comorbid depression, I might lean more towards utilizing medications like duloxetine and venlafaxine.

NVA: How do you determine when you've reached a therapeutic dose of a medication?

Dr. Wasserman: Each medication type and dosage must be individualized to the patient. Everyone metabolizes medications differently. In fact, two of my patients – one taking 10mg and the other 75mg of amitriptyline – have had equally positive decreases in pain. It's really important for practitioners involved in the pharmacological management of vulvodynia to understand that one cannot characterize a medication trial as a "failure" until the dose is titrated up to a therapeutic level and the patient stays at that dose for upwards of four to eight weeks, depending on the medication. I can't tell you how many patients I've seen over the years who report "failing" various medication trials in the past, but do very well with the same medication when I titrate it to the higher therapeutic dose for a longer trial period. Equally important is that I have to start many of my vulvodynia and other pain patients on very tiny doses, and gradually, in

See PHARMACOLOGICAL, page 9

Pharmacological

(from page 8)

very small incremental steps, increase the dose to a therapeutic level. Most clinicians make the mistake of starting pain patients on the dose recommended on the package insert, which is most often too high, causing patients to stop using it prematurely due to intolerable side effects.

NVA: What new medications are on the horizon?
Dr. Wasserman: Various physiological pathways involved in pain perception are targets of medications currently being developed and studied to treat chronic pain disorders, including vulvodynia. These include drugs targeting peripheral nerve TRPA1 receptors, and drugs that target nerve growth factor or nerve growth factor receptors in peripheral nerves. Although it may be quite some time before these drug candidates are FDA-approved, new medications targeting already well known pain modulating receptors are already available. One example is the opioid tapentadol, which may be particularly useful in the treatment of chronic neuropathic pain states, because it does not rely solely on its opioid effect. Rather, tapentadol, like the SNRI drugs, blocks the reuptake of norepinephrine. In fact, the long-acting formulation of the medication is the first opioid to ever be approved specifically for the treatment of a neuropathic pain state – diabetic neuropathy in this case. There are also relatively new drugs that bind the cannabinoid receptors, which appear to have efficacy in treating various chronic neuropathic pain states. Nabilone and Sativex are two such medications, although the latter is not currently approved for use in the U.S. Even some non-traditional nutraceutical herbal-type agents may show varying degrees of effectiveness in multiple chronic pain states. Such compounds include 5-HTP, a serotonin precursor, and even Omega-3 fish oil, for which some studies show improvements in painful inflammatory conditions. When very poor non-restorative sleep is felt to be a strong comorbid factor in certain chronic pain states, the drug sodium oxybate (i.e., GHB) may even have some benefit. It's been shown in multiple studies to be beneficial for both sleep disorder and fibromyalgia pain, though it is not currently FDA approved for fibromyalgia.

NVA: How effective are the medications you discussed in managing vulvodynia symptoms?
Dr. Wasserman: The vast majority of women – even those with severe vulvodynia – can achieve reasonable pain management with the right medication or combination of medications. Because we don't yet have a full understanding of all the underlying mechanisms responsible for different vulvodynia subtypes and because everyone responds differently to medications, it usually takes some time to experiment with different medication classes, as well as different medications in each class, before finding one or more that work best for each patient. Also, I don't want to imply that pharmacological management is the only way to treat vulvodynia. In fact, there are many integral components of a multidisciplinary treatment plan for any chronic pain syndrome, including vulvodynia. One example is counseling, which helps pain sufferers improve coping and self-management skills, including becoming better able to emotionally tolerate pain.

NVA: What other treatments do you recommend for women with vulvodynia?
Dr. Wasserman: I cannot overemphasize how important it is for patients with any chronic pain condition, including vulvodynia, to maintain a healthy lifestyle. This includes trying to keep stress levels down, because stress is well-known to increase pain perception. There are numerous therapies – relaxation techniques, meditation, tai chi, biofeed-

See PHARMACOLOGICAL, page 10

Pharmacological

(from page 9)

back and self-hypnosis just to name a few – that can play an important role in pain management. I am a strong advocate of all pain patients, particularly those that may have a centralized component to their pain condition, engaging in regular aerobic exercise, because it's been shown to increase serotonin levels. Low serotonin levels have been correlated with various chronic pain conditions such as fibromyalgia, as well as depression and anxiety. Additionally, regular exercise simply helps build self-esteem, empowerment and a mental perception of health and vitality, all of which undoubtedly help people better cope with chronic illness. I'm also intrigued by the possibility of diet affecting pain perception and the potential benefit of the "anti-inflammatory diet" (i.e., the Mediterranean diet) in promoting general health, vitality, longevity and perhaps even improved pain control.

NVA: What recommendations do you have for women with vulvodynia who experience painful sex?

Dr. Wasserman: Painful sex, or dyspareunia, is one of the unfortunate consequences of vulvodynia that many sufferers experience. In my clinical experience, treating this symptom can often be very difficult for a variety of reasons. Even in many patients in which I've been able to successfully manage their "resting" baseline pain (i.e., the pain they experience with no direct vaginal manual stimulation), it can be very difficult for these women to comfortably engage in intercourse. It is not exactly clear why this is the case, though there may be multiple bio-psycho-social reasons. Many women who have had vulvodynia for many years, and who have abstained from sexual activity as a consequence of this, may have a deeply embedded fear of engaging in sex. Understandably, they may fear that intercourse will reinitiate their symptoms. Some women have had success using dilator therapy, in which they "simulate" intercourse at their own pace using hand-held dilators, while slowly advancing the diameter of successive dilators. In this way, women can control the pace in which they advance this "simulated" intercourse, as well as the amount of force of the stimulation, and only attempt "real" intercourse when they feel confident that they can tolerate such activity. I've had patients who've successfully used this intervention, eventually engaging in gratifying sexual intercourse with their partners.

Juraskova and colleagues recently published a study looking at the usefulness of a combination therapy termed "OVERcome (Olive Oil, Vaginal Exercise, and MoisturizeR)" in decreasing painful sex in women with breast cancer. Women in this study were instructed to perform specific pelvic floor relaxation exercises, use a certain type of vaginal moisturizer and to use olive oil as a lubricant during sex (5). After 12 weeks, this intervention resulted in significant improvements in the study participants' dyspareunia, sexual function and quality of life. This approach is a safe and potentially effective modality, certainly worth attempting in patients with vulvodynia who experience significant pain with sex. It would be interesting to perhaps study whether there is potential for the newly FDA-approved treatment ospemifene (Osphena), a selective estrogen receptor modulator for women with post-menopausal dyspareunia, to help women with vulvodynia whose pain with intercourse may also result from vaginal and vulvar tissue atrophy, which the treatment targets. [*Editor's Note: For more information on the approval of ospemifene, please see the Q&A with Dr. Gloria Bachmann in the summer 2013 issue of* NVA News*, available at www.nva.org/order_newsletters.htm*.]

See PHARMACOLOGICAL, page 11

Pharmacological

(from page 10)

NVA: How likely is it for women with vulvodynia to improve with treatment?

Dr. Wasserman: With a combination of sophisticated rational medical management targeting various biological pathways involved in chronic pain modulation, along with healthy lifestyle changes and activities that promote self-empowerment and coping strategies, I've been able to help many women with vulvodynia achieve significant pain control. As a physician, it's very gratifying to see so many patients' function and quality of life improve so dramatically once their pain is well-controlled, as well as the impact that this has on their loved ones and friends. As new treatment approaches and strategies emerge from the increasing amount of research taking place, I feel even more hopeful about our ability as a medical community to help women with vulvodynia achieve effective pain control and improved quality of life.

References

1.Ventolini G, Gygax SE, Adelson ME, Cool DR. Vulvodynia and fungal association: a preliminary report. M*ed Hypotheses*. 2013 Aug:81(2):228-30.

2.Mayer, E. Chronic Visceral Pain: The Long Path to Better Treatments. *Global Year Against Pain Lecture* presented at the American Pain Society Annual Meeting. May 2013, Tampa, FL.

3.Wager TD, Atlas LY, Lindquist MA, Roy M, Woo CW, Kross E. An fMRI-based neurologic signature of physical pain. *NEJM*. 2013; 368:1388-1397.

4.Hampson JP, Reed BD, Clauw DJ, Bhavsar R, Gracely RH, Haefner HK, Harris RE. Augmented central pain processing in vulvodynia. *J Pain*. 2013 Jun;14(6):579-89.

5.Juraskova I, Jarvis S, Mok K, Peate M, Meiser B, Cheah BC, Mireskandari S, Friendlander M. The acceptability, feasibility, and efficacy (phase I/II study) of the OVERcome (Olive Oil, Vaginal Exercise, and MoisturizeR) intervention to improve dyspareunia and alleviate sexual problems in women with breast cancer. *J Sex Med*. 2013 Oct;10(10):2549-58. ■

Tissue Changes

(from page 1)

Although Provoked Vestibulodynia (PVD, formerly vulvar vestibulitis syndrome) is thought to be the leading cause of painful sex in reproductive-aged women, it's been poorly described in menopausal women. This is likely because all pain associated with sexual activity after menopause is assumed to be related to atrophic skin, resulting from aging and hormonal changes. Even so, research demonstrates that many women continue to stay sexually active through the menopausal transition and share the same concerns as premenopausal women regarding vulvovaginal pain, painful sex and related dysfunction. Because vulvovaginal estrogen deficiency results in lubrication and arousal difficulties, women often treat symptoms with estrogen supplementation or lubricants, yet when sex continues to cause pain, a PVD diagnosis is often not considered. Kao and colleagues reported that 95 percent of menopausal women with dyspareunia also had localized provoked pain in the vestibule despite the use of hormone supplements in one-third of patients (1). Persistent vulvar pain after estrogen treatment in menopausal women merits evaluation for causes beyond vulvovaginal atrophy.

With prior NVA grant support, our group conducted an analysis of nearly 90 vestibular tissue specimens from premenopausal women under-

See TISSUE CHANGES, page 13

In Her Own Words

By Lyn F.

Lyn is a wife, mother and self-employed commercial artist. She experienced an allergic reaction to Macrobid that left her with Generalized Vulvodynia in 1993. As an NVA support contact, she learned to speak openly and frankly about a very private condition, and realized that the most empowering thing for sufferers is to know that they are not alone.

Vulvodynia can be a lonely affliction. When I was diagnosed I informed the women in my family, because I developed vulvodynia as a result of an allergic reaction to Macrobid and I didn't want them to suffer a similar fate. Afterwards, they never inquired about my progress in getting treatment. It is simply something many people don't want to know about you. My husband and best friend have been my rocks. When I had no credibility with the various doctors I saw, I always had it with them. If I didn't have their understanding, I would have doubted my sanity. I've come to know that my husband truly loves me. We were unable to be intimate for two years and he never made demands of me or lost his patience. In fact, he became my patient advocate. I always felt that it was my usefulness that made me worthy of affection, but I was wrong.

For 15 years, I found relief from vulvodynia with Zoloft. But once I reached menopause, the drug was no longer effective. So now I am going through drug trials again. Exercise helps. Walking releases endorphins and helps me keep depression at bay. Patience is key. Although I'm currently uncomfortable, because I found a solution before, I know that another one is out there for me. I just have to find it!

Vulvodynia has made me a stronger person. Through everything, I worked full time, took care of my family and elderly relatives and even started an after-school program for the PTA, all while in searing pain. If I can do that, I know that I can handle anything. I'm now better-equipped to handle the typical aches and pains that come with aging. Healthy people are bowled over by such things, but I take them in stride because most of these pains are temporary as opposed to the constant pain of vulvodynia. So my knees hurt when I crouch down to get something – big deal! When the tasks at hand seem overwhelming, I break them down into smaller pieces. I tell myself, "Just make the bed and see how it goes. Just fold the laundry and take a break." I concentrate on one foot in front of the other, not the finish line.

Be a warrior for yourself! As a phone support person, I found a few women who were too willing to sink into despair and helplessness. You need to educate yourself so you can speak intelligently with your doctor. You need to be open to any solution. I have spoken to a number of women who dismiss certain therapies based on fear. There is no one-size-fits-all solution for vulvodynia. I had read in a prior *NVA News* article that Zoloft doesn't help most people with chronic pain, including vulvodynia, yet it kept me pain free for 15 years! You don't know what works until you try. Go into the doctor's office with a written list of questions. Bring them articles you have found. Let them know that you are proactive and not willing to give up and go away. And if they throw up their hands and say they can't help you (that happened to me!) then ask them to tell you who can. And when nobody else does, believe in yourself! ■

Tissue Changes

(from page 11)

going vestibular surgery, comparing those taken from women with the primary and secondary forms of PVD. [*Editor's note: See page 2 for definitions of these subtypes*.] We found that both subgroups had features of neurogenic inflammation, which arises from the release of inflammatory substances from a certain type of peripheral nerve. It is characterized by abundant lymphocytes (white blood cells) and mast cells (connective tissue cells that release histamine during an allergic or inflammatory response), as well as an increase in both the number and size of nerve fibers. Vestibular tissue specimens from women with primary PVD had significantly more nerve proliferation than did tissue from women with the secondary subtype, who in turn had more lymphocytes. [*Editor's note: See the Fall 2010 issue of* NVA News *for a detailed summary of this study and its findings.*]

With some grant support from the NVA, along with federal funding from the Eunice Kennedy Shriver National Institute of Child Health and Human Development and the Office of Research on Women's Health, we recently repeated this study in 21 postmenopausal women with secondary PVD, and compared tissue findings to those from premenopausal women in our prior study. By doing so, we hoped to differentiate between pre- and post-menopausal women, and provide insight into the underlying mechanisms of the disorder.

All 21 postmenopausal patients had secondary PVD. The majority (71%) reported first experiencing painful sex when their estrogen levels dropped, although for some, this pain started prior. Painful sex was one of the initial symptoms developed during the menopause transition for half of the women. Two women developed symptoms following childbirth, which never resolved, and they waited to seek medical care until menopause. Two developed painful sex in their premenopausal years, which worsened with menopause. One-third had symptoms that didn't seem to correlate at all with estrogen loss. At the time of surgery (when the vestibular tissue samples were collected), all but three women were using some form of supplemental estrogen (mainly systemic administration), 10 women were using systemic progestins for endometrial protection, and only three were not using any hormones as a result of breast cancer or personal choice.

Multiple tissue features were different in the postmenopausal patients compared with our previously described premenopausal series. Overall, we found that vestibular tissue from pre- and postmenopausal women with PVD shares histologic features of neurogenic inflammation but differs in degree. Postmenopausal tissue specimens showed more severe chronic inflammation (lymphocytes and mast cells) than either premenopausal group and less nerve fiber proliferation than premenopausal primary PVD counterparts. The duration of symptoms did not correlate with increased inflammation; the group with the least inflammation was the group with the longer duration of symptoms (primary premenopausal). Estrogen receptor expression was not statistically different among all groups, perhaps as a result of varied supplemental hormone regimens

See TISSUE CHANGES, page 14

Tissue Changes

(from page 13)

used by patients in all groups.

The study is descriptive and does not prove causation. There are several limitations that impede our ability to draw conclusions from this study. Since this was an analysis of tissue we had collected from patients in the past, we did not have a uniform measure of the degree of vulvovaginal atrophy (i.e., thinning of the vaginal and vulvar tissue). The ability to perform an ad hoc power analysis was limited because no single tissue feature defines PVD. Another limitation was lack of uniformity of clinical histories and hormone use. We also did not collect blood to analyze and compare circulating levels of estrogen. Since the study group was small, we weren't able to stratify groups based on the type of estrogen administration used (e.g., systemic, topical), however, when we analyzed the data after excluding the women who were not taking any form of estrogen, the results didn't differ.

Findings from this and other studies suggest that in some women, declining estrogen levels may trigger the development of PVD. Although the mechanism(s) of PVD remains unclear, understanding the change in hormonal environment as it correlates to the development of these tissue patterns may help researchers understand the mechanisms responsible for the initiation and/or persistence of certain PVD subtypes. The majority (71%) of the patients in our menopausal group noted the onset or worsening of pain related to loss of estrogen, either during the menopausal transition or with prior estrogen loss following childbirth. Twenty-two percent of the premenopausal secondary PVD sufferers reported the advent of pain during the postpartum period. In these women, we suspect there is a relationship between hormonal signaling in the vestibule and neurogenic inflammation characteristics of PVD.

Menopausal estrogen supplementation achieves only low levels of estrogen when compared with the range of physiologic circulating estradiol in premenopausal women. The postmenopausal group had the greatest number of lymphocytes and mast cells of all groups, perhaps indicating that these cells respond most strongly to low estrogen levels, stimulating nerve growth/sprouting in the vestibule. When estrogen supplementation does not alleviate painful sex after menopause, it may indicate that supplementation is being utilized too late, or inadequately, and therefore cannot stop tissue changes from occurring. The inflammatory response may continue to stimulate nerve proliferation, leading to PVD.

This hypothesis is supported by published studies by Smith and colleagues who reported the association of low estrogen levels and nerve proliferation in vaginas of rats and in the upper genital tracts of mice (2, 3). When estrogen levels are at their lowest in rats, nerves proliferate, and as their reproductive cycle changes and estrogen levels rise, these nerves retreat. This pattern repeats cyclically. If the same pattern occurs in the human vestibule, this phenomenon may explain menopausal PVD. Despite the common description of estrogen supplementation as "estrogen replacement," it is meant to be low-dose rather than "replacement" therapy, and vestibular tissue levels may not achieve a threshold that prevents or treats vestibular sensitivity. In reviewing current medical literature, no investigators have compared vestibular tissue from women with painful sex associated with menopause prior to and following the administration of estrogen supplementation, probably because estrogen therapy eliminates symptoms in so many postmenopausal women. However, there may be an estrogen threshold that varies from woman-to-woman for the presumed

See TISSUE CHANGES, page 15

Tissue Changes

(from page 14)

nerve changes to recede. As Kao suggests, the common occurrence of vulvovaginal atrophy does not adequately explain the findings of vestibular pain (4, 5). In 95 percent of their postmenopausal study group with vestibular pain and painful sex, women used a variety of estrogen supplements; the degree of atrophy varied, but vestibular pain persisted (1).

A PVD diagnosis should be considered in both pre- and postmenopausal women who experience painful sex, as it affects women of all ages. Although supporting the menopausal patient with adequate estrogen, either through local or systemic administration, is an important clinical consideration, it may not be effective in alleviating painful symptoms. Women who are suffering from painful intercourse should first talk to their providers about the use of local estrogen. Daily estrogen cream applied directly to the vestibule may support the tissue and adequately relieve vestibular pain in peri- or postmenopausal women. Although many hormone formulations are designed to support only the vagina (e.g., Vagifem® tablets or Estring® vaginal ring), directly targeting the vestibule may better treat the tender tissue. If after using estrogen supplementation and generous lubrication, a woman is still experiencing vestibular pain and painful sex, a clinical exam to investigate PVD diagnosis is warranted.

[*Editor's note: The results of this study are described in full in: Leclair CM, Goetsch MF, Li H, Morgan TK. Histopathologic characteristics of menopausal Vestibulodynia.* Obstet Gynecol. *2013 Oct;122(4):787-93.*]

Selected References

1. Kao A, Binik YM, Amsel R, Funaro D, Deroux N, Khalife S. Biopsychosocial predictors of postmenopausal dyspareunia: the role of steroid hormones, vulvovaginal atrophy, cognitive-emotional factors, and dyadic adjustment. *J Sex Med* 2012;9:2066–76.

2. Ting AY, Blacklock AD, Smith PG. Estrogen regulates vaginal sensory and autonomic nerve density in the rat. *Biol Reprod* 2004;71:1397–404.

3. Zoubina EV, Smith PG. Sympathetic hyperinnervation of the uterus in the estrogen receptor alpha knock-out mouse. *Neuroscience* 2001;103:237–44.

4. Kao A, Binik YM, Kapuscinski A, Khalife S. Dyspareunia in postmenopausal women: a critical review. *Pain Res Manag* 2008;13:243–54.

5. Kao A, Binik YM, Amsel R, Funaro D, Leroux N, Khalife S. Challenging atrophied perspectives on postmenopausal dyspareunia: a systematic description and synthesis of pain characteristics. *J Sex Med Ther* 2012;38:128-50. ■

Grants

(from page 6)

this application is to examine the sensory and functional characteristics of women with postpartum pelvic pain (somatic-musculoskeletal pain) and interstitial cystitis/CPP (visceral pain), compared to women without CPP. Additionally, we will initiate preliminary investigation into the central brain imaging of these CPP subtypes. Our central hypothesis is that women with varying types of CPP will demonstrate unique peripheral (sensory and functional) and central characteristics specific to their diagnoses and their underlying mechanisms. The expected outcome of this study is the delineation of the clinical and scientific assessment methods that most accurately reflect the underlying peripheral and potential central mechanisms driving CPP subtypes. The public health impact of this work will be to enable clinicians to provide more timely and targeted interventions for women with CPP. ■

Research Participants Needed for Vulvodynia Study

We are seeking the following research participants for a study of pain thresholds:
* Healthy women without any type of chronic pelvic pain condition (control subjects)
OR
* Women with a diagnosis of vulvodynia

All women must be between the ages of 18 and 50

Requirements of this research study will include:
Collection of questionnaires
Blood sample collection
Sensory testing (touch, heat/cold and vibration) of the external genitalia

This study requires two visits and each visit will last approximately two hours.
You will be compensated $50 for each visit.

For additional information please contact:
Amber Surian
By email: aas64@georgetown.edu
By phone at: 202-444-1210

UCLA Center for Neurobiology of Stress (Los Angeles, CA)
UCLA Brain Imaging Study

If you are female between the ages of 18 to 55 and have been diagnosed with vestibulodynia or vulvodynia OR are experiencing chronic pain at the opening of the vagina or at the area surrounding the opening, with or without intercourse, we would like you to participate in a research study. This study is conducted by Dr. Jennifer Labus at the UCLA Oppenheimer Center for Neurobiology of Stress (www.uclacns.org) and Dr. Andrea Rapkin at the Department of Obstetrics and Gynecology.

Earn up to $130 for your participation. The purpose of this research is to help understand the physiology and genetic makeup of this chronic pain condition. Participation involves 2-3 visits (1 screening, 1 exam, 1 MRI scan) and several questionnaires over approximately 1-3 weeks. You must be right-handed and not pregnant.

Contact: Study coordinator at 310-825-5255