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Pharmacological Treatment of Vulvodynia

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Dysesthetic vulvodynia, or generalized vulvar dysesthesia (hereafter referred to as "vulvodynia"), is a disorder whose treatment has traditionally been contemplated using the typical neuropathic pain model. In fact, some doctors inter-changeably refer to vulvodynia as "pudendal neuralgia"—implying that the condition is simply a type of peripheral nerve dysfunction or "neuralgia." Furthermore, since vulvodynia is commonly perceived to be a neuropathic pain disorder analogous to conditions such as diabetic neuropathy, it stands to reason that various treatments and medications commonly used to treat neuropathic pain should be effective in the treatment of vulvodynia. The problem with this treatment approach is that it is anything but clear whether vulvodynia is a neuropathic pain disorder.

The primary reason why many doctors and scientists presume that vulvodynia is a neuropathic pain disorder is that patients usually report a painful vulvar burning sensation and vulvar allodynia (a condition in which normally non-painful stimuli, such as touch, induce pain). Of course, it is true that many neuropathic pain conditions, such as diabetic neuropathy and post-herpetic neuralgia, do present with burning-type pain and allodynia. However, this alone does not definitively prove that vulvodynia is a neuropathic pain disorder. In fact, other non-neuropathic pain disorders, including various inflammatory and infectious conditions, can present with burning pain and allodynia. Even fibromyalgia, a non-neuropathic and

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Recent Findings on Vulvar Vestibulitis Syndrome

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In recent years, physicians and scientists have shown greater interest in vulvodynia leading to exciting new research in the area of Vulvar Vestibulitis Syndrome (VVS). The latest research findings on the diagnosis, treatment and etiology of VVS were presented at the 2001 ISSVD meeting. This article will review the VVS studies presented at the conference and the results of other recently published studies in the field.

DIAGNOSIS

In current practice, VVS is diagnosed on the basis of three criteria established by Dr. Eduard Friedrich, Jr. These criteria are: (1) severe pain during attempted vaginal entry; (2) tenderness to pressure localized in the

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NVA Presents at Women's Health and Pain Conferences

During the past four months, the NVA organized presentations on vulvodynia at two important medical conferences. In January 2002, Christin Veasley, the NVA's director of professional programs, conducted a session on vulvodynia at the annual meeting of the American Medical Women's Association (AMWA) in San Antonio, Texas. The AMWA conference covers many topics relevant to women's health, including hormone replacement therapy, urinary incontinence, ovarian cancer, chronic fatigue syndrome, irritable bowel syndrome and osteoporosis. The NVA's support group leader from Wisconsin, Jane Elmer, volunteered her time to help Christin at the NVA exhibit booth. (Thank you, Jane!) They disseminated our brochures and newsletters and spoke with hundreds of medical professionals involved in women's health.

In March 2002, Christin chaired a symposium at the American Pain Society's (APS) annual conference in Baltimore, Maryland. NVA medical advisory board members, Doctors David Foster and Ursula Wesselmann, together with Dr. Allan Gordon, director of the Wasser Pain Management Centre in Toronto, participated in the symposium. The 90-minute presentation covered potential causes, diagnosis, and treatment of vulvodynia. Christin gave a historical overview of vulvodynia and described to the audience how the disorder affects women's quality of life. She also reported on vulvodynia research funding by the National Institutes of Health and recent publicity initiatives undertaken by the NVA. Dr. Wesselmann reviewed key publications in the medical literature on diagnostic criteria for Vulvar Vestibulitis Syndrome (VVS) and reviewed treatment options for both VVS and dysesthetic vulvodynia. Dr. Foster summarized the findings of recent research studies on VVS and described his current work on the possible etiology of the disorder. Dr. Gordon's presentation on clitorodynia (clitoral pain) began with a description of the physiology of the clitoris. He then reviewed the few medical articles written on the subject, described the results of a survey he conducted in his clinic and presented case studies of women with this very painful variant of vulvodynia. (For more on clitoral pain, see Dr. C. Paul Perry's article in the Fall 2000 issue of *NVA News*.)

In addition to the symposium, the NVA also staffed an exhibit booth at the APS conference. Executive board members Catherine Clevenger and Jeanmarie Dunn assisted Christin in providing information and distributing educational materials on vulvodynia. They used the opportunity to speak directly with pain specialists about the importance of pain management in the treatment of vulvodynia. Among other visitors to our booth were several representatives from pharmaceutical companies who expressed interest in including vulvodynia patients in upcoming clinical trials of new pain medications.

In addition to its patient services, the NVA is committed to educating medical professionals in varied specialties about vulvodynia and will continue to organize presentations and exhibit at medical meetings throughout the year. The next conference on our schedule is the 10th Annual Congress on Women's Health, to be held in Hilton Head, South Carolina in May 2002. ■

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non-inflammatory pain condition, can exhibit burning pain as well as tingling, numbness, and diffuse allodynia, symptoms commonly associated with neuropathic pain. Many also maintain that because vulvodynia can sometimes be successfully treated with tricyclic antidepressants (e.g., amitriptyline), drugs commonly used to treat neuropathic pain conditions, vulvodynia must therefore also be a neuropathic pain condition. However, many non-neuropathic pain conditions, including chronic tension headaches, myofascial pain, temporomandibular dysfunction, fibromyalgia, and even various forms of non-neuropathic cancer pain, also may respond favorably to tricyclic antidepressants.

The truth is, there is no evidence of specific nerve damage or dysfunction causing the symptoms of what is known as vulvodynia. Indeed, there is some indication that vulvodynia does not always behave like a typical neuropathic pain condition. In many true neuropathic pain conditions, such as diabetic neuropathy and trigeminal neuralgia, the pain is commonly confined to at least the general region of where the nerve damage or dysfunction is present. Yet, some vulvodynia patients complain of more diffuse pain, often present in the entire vulvar region, the anus, the rectum, the bladder, the inner thighs, and so forth. These varying painful anatomic regions do not correspond to any one specific dysfunctional nerve or closely linked group of nerves.

It is well-known among practitioners who treat vulvodynia that many of these patients suffer from more widespread body pains, in areas such as the upper and lower extremities, cervical and lumbar spinal regions, and so forth, that are more reminiscent of fibromyalgia than of any localized neuropathic pain condition. In my clinical practice, I have encountered multiple patients presenting with a primary complaint of vulvar pain but, upon questioning and physical examination, they easily meet the American College of Rheumatology criteria for the diagnosis of fibromyalgia—including long-standing widespread body pain and at least eleven fibromyalgia tender points on physical examination. Many vulvodynia patients also suffer from various ailments commonly associated with fibromyalgia such as irritable bowel syndrome, fatigue, sleep disorder, interstitial cystitis, depression, and multiple chemical sensitivities.

Related Disorders

The idea that a seemingly localized pain disorder such as vulvodynia might be related to a more generalized condition such as fibromyalgia is not a novel concept. In fact, a recent study presented at the 2002 American Pain Society meeting in Baltimore, Maryland showed that 40 percent of those with a diagnosis of temporomandibular dysfunction (i.e., TMD or "TMJ syndrome"), a supposedly localized pain disorder, also meet the accepted criteria for fibromyalgia syndrome. Likewise, 40 percent of those with a diagnosis of fibromyalgia also meet the criteria for TMD. The common co-morbidity (co-existence) of the two disorders was so profound that the authors called into question the idea that fibromyalgia and TMD are actually two separate disorders. Indeed, their data seem to indicate that TMD and fibromyalgia may actually be different physical manifestations of the same underlying central pain-processing disorder.

Certainly, it is possible that at least some types of vulvodynia are related to fibromyalgia in the same way that TMD may be. Of course, to suggest such a relationship at this time is merely theoretical since, to my knowledge, there is no scientific data that examines the co-morbidity of vulvodynia with any other pain syndromes. Nevertheless, until such a study proving otherwise is done, it is my contention that many, if not most, cases of vulvodynia are not primary neuropathic pain conditions, but rather, are part of a more generalized condition possibly related to fibromyalgia. If such a proposition proves to be true, then the best pharmacological treatments for vulvodynia may be quite different than what was assumed to be the case using the neuropathic pain model of vulvodynia. It must also be kept in mind that future studies may show that not all cases of vulvodynia are of the same cause; some cases may be truly neuropathic in nature, and should be treated the same way that other neuropathic pain conditions are treated—namely, by using anti-neuropathic pain drugs such as gabapentin (Neurontin) and carbamazepine (Tegretol).

Considering this proposed paradigm, however, physicians who treat vulvodynia pharmacologically may want to re-examine how they approach the treatment

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of such patients. Common pharmacological treatments used for neuropathic pain, although their mechanisms of action vary and are not fully understood, are generally thought to work by acting directly on the peripheral and/or central nervous system to prevent abnormal propagation of impulses through the sensory nervous system. For example, in the case of trigeminal neuralgia, it is thought that Tegretol decreases pain by blocking sodium channels in nerve cells, thereby stabilizing abnormally firing pain-producing neurons. However, if one makes the assumption that vulvodynia is not caused by abnormally firing sensory nerves, one can expect that a drug such as Tegretol or Neurontin will not be effective.

Central Sensitization

Where the issue of causality of vulvodynia becomes even more complicated is the fact that all chronic pain conditions, regardless of whether they begin as true neuropathic pain conditions (e.g., trigeminal neuralgia) or not (e.g., TMD), can induce a central nervous system pathological process known as central sensitization. In central sensitization, various components of the central nervous system, including the spinal cord, the brain stem, and the brain itself, become abnormally sensitized to either perceive or, in some cases, even induce higher levels of pain. Various neurochemical and neuro-physiological processes occurring in the central nervous system create this effect.

In this sense, the concept of central sensitization unifies almost all chronic pain syndromes—whether they begin as primary neuropathic pain syndromes or not. Therefore, if pharmacological treatments can be developed which reverse or prevent the process of central sensitization, then such treatments may prove beneficial for both neuropathic and non-neuropathic chronic pain syndromes alike. Indeed, this treatment approach seems to have proven useful in the treatment of fibromyalgia. It has been shown in multiple well-controlled studies that many patients with fibromyalgia have abnormally low levels of serotonin and elevated levels of substance P (a neurotransmitter that stimulates pain receptors) in their cerebral spinal fluid. These neuro-chemical abnormalities are believed by many to be somehow related to the abnormal central pain processing (i.e., central sensitization) evident in fibromyalgia. As such, medications that partially act to elevate neural serotonin levels, such as tricyclic antidepressants, have been used for the treatment of the disorder. Indeed, well-controlled studies have confirmed the usefulness of such drugs in the treatment of fibromyalgia. Likewise, it is possible that similar central neuro-chemical abnormalities also exist in vulvodynia, whether the vulvodynia is due to a primary neuropathic process or not.

Other sites of possible pharmacological intervention exist in various chronic pain syndromes that could also potentially benefit vulvodynia patients. One very prominent concept being widely studied in the chronic pain scientific community is the idea of N-methyl-D-aspartate (NMDA) receptor-mediated central-sensitization. Indeed, a growing body of scientific evidence now exists showing the important role that the NMDA receptor mechanism in the dorsal horn of the spinal cord plays in the perpetuation of central sensitization and, therefore, many types of chronic pain—presumably including vulvodynia. It is the over-stimulation of these receptors by the excitatory neurotransmitter glutamate that seems to be responsible for this process. One of the goals of pain researchers is to find medications that can either reverse or prevent this process by either blocking or shutting down the NMDA receptor complex.

Although better NMDA receptor antagonist medications (medications that block the NMDA receptor mechanism) need to be developed, a few such medications do currently exist. Unfortunately, the available NMDA receptor antagonists are either very poorly tolerated, very weak in potency, or both. An example of such a medication is dextromethorphan, an ingredient found in common cough syrups. Although multiple studies have suggested some efficacy of dextromethorphan in the treatment of various pain states, it is often only marginally effective, if effective at all, and it is sometimes poorly tolerated in the high doses that are often necessary to achieve the desired effect. Other medications that have NMDA receptor-antagonizing effects are Ketamine, an even more poorly tolerated medication than dextromethorphan, and methadone, an opioid pain reliever that can be very effective in both neuropathic and non-neuropathic chronic pain states.

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Individualized Treatment

If nothing else is certain about vulvodynia, it should be abundantly clear from the above summary that vulvodynia, like any other type of chronic pain syndrome, is a very complicated disorder that probably has multiple causes and may not even be a single definable entity. Keeping this in mind, it is my belief that the best approach to the pharmacological treatment of vulvodynia is to individualize each patient's treatment. This can only be accomplished through a thorough evaluation, incorporating a meticulous history, physical examination, and appropriate laboratory examination. Obviously, all common treatable gynecological and dermatological conditions must first be ruled out. Once it is determined that such conditions are not present, practitioners should seek clues as to whether the patient suffers from a more generalized condition.

For instance, if a patient who presents with vulvar pain has either a current or past history of diffuse body pain, TMD, sleep disorder, multiple chemical sensitivities, and/or irritable bowel syndrome, then she may actually be suffering from a fibromyalgia-type disorder and may benefit from medications known to be effective for fibromyalgia. Likewise, if a patient presents with very diffuse pain, complaining of discomfort in multiple sites such as the vagina, vulva and lower abdomen, then she is probably not suffering from a true neuropathic pain condition. Rather, she may have developed a central sensitization disorder, manifesting primarily as chronic pelvic and vulvovaginal pain. Medications that potentially reverse the central sensitization process may be helpful in such patients. If a patient presents with a more localized, possibly even unilateral, burning- or shooting-type pain in either the vagina, vulva or clitoris, then this may actually be a true neuropathic pain process. In such a patient, it may be prudent to begin treatment with a typical anti-neuropathic pain medication such as Neurontin.

Antidepressants

Some medications can effectively treat both neuropathic and non-neuropathic pain conditions. Examples of such drugs are both tricyclic antidepressants and extended-release venlafaxine (Effexor XR). These antidepressant medications may be ideally suited to treating vulvodynia, a condition that may or may not have neuropathic pain components. What makes these two classes of drugs different from the more commonly prescribed selective serotonin reuptake inhibitors (SSRIs), such as Prozac, is the fact that they also block the reuptake of norepinephrine, a neurotransmitter which seems to be critical in the modulation of pain.

Effexor XR has several advantages over the older tricyclics. Most importantly, this medication is not associated with the cardiac toxicity inherent in the tricyclics, which can lead to death in overdose. This is particularly important when treatment is rendered to extremely depressed patients who could potentially attempt suicide. In addition, Effexor XR does not possess the troublesome side effects so common with tricyclics due to their anti-cholinergic, anti-adrenergic, and antihistaminic effects. These are the mechanisms responsible for the tricyclics' often cited negative effects of dry mouth, constipation, urinary retention, weight gain, sedation and orthostatic hypotension (a fall in systolic blood pressure upon standing). Effexor XR also is not associated with as many troubling drug-drug interactions as the tricyclics.

An increasingly large body of scientific evidence is emerging which substantiates the efficacy of Effexor XR in the treatment of various neuropathic and non-neuropathic pain conditions such as diabetic neuropathy and fibromyalgia. A key point worth noting is that both studies and anecdotal evidence indicate that Effexor XR must be taken in fairly high doses—at least 150 mg, in order to achieve a pain-fighting effect. Interestingly, there is evidence that 150 mg is the minimum dose in which norepinephrine reuptake inhibition begins to take place, providing further evidence that norepinephrine reuptake inhibition is a critical factor for an antidepressant's ability to provide pain relief. Of course, Effexor XR comes with its own array of possible side effects—namely, sexual dysfunction, sleep disturbances, gastro-intestinal side effects such as nausea, and, less commonly, elevation in blood pressure (though this effect seems to occur at mostly higher dosages—above 300 mg). By and large, however,

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these side effects are generally better tolerated than those of tricyclics.

Effexor XR is also an extremely potent antidepressant medication useful in treating chronic pain patients who also suffer from depression. Tricyclics, on the other hand, are not as useful for depression when used in the low doses commonly used to treat chronic pain. In fact, some studies indicate that Effexor XR may be a more effective antidepressant than the SSRI medications. Effexor XR also has an activating effect in some people that may be useful in chronic pain patients who also suffer from an element of fatigue.

One possible advantage of using tricyclics rather than Effexor XR is that they appear to have a nerve cell sodium channel-blocking effect that may be useful for the treatment of neuropathic pain. In choosing a tricyclic antidepressant, the second and third generation tricyclics, nortryptiline and desipramine, may be better tolerated than amitriptyline in some patients. Interestingly, a new drug by Eli Lilly that acts similarly to Effexor XR, but may be even more potent in the treatment of pain, may be approved soon.

Based on the history and physical examination, if a patient's vulvodynia presents with at least some indication that a neuropathic component is responsible, successive trials of various anti-neuropathic pain medications may be warranted. Of course, even this scenario may warrant an initial trial of either a tricyclic antidepressant or Effexor XR, since both can be effective for neuropathic pain. This makes particular sense if the patient also suffers from depression.

Anticonvulsants

Another option is to start with a specific anti-neuropathic pain medication such as Neurontin, an anticonvulsant medication that is extremely safe and generally well tolerated. Neurontin has proven to be effective in both post-herpetic neuralgia and diabetic neuropathy, two well-known neuropathic pain conditions. Some of Neurontin's advantages are its lack of drug-drug interactions, its lack of metabolism by the liver, and its safety in over-dose. On the other hand, it does possess its own potential "annoyance" side effects of dizziness, sedation, weight gain, peripheral edema, and occasional cognitive dysfunction. However, if the drug is slowly titrated to the minimal effective dose, then most of these side effects can usually be either eliminated or greatly reduced. It is critical to note here that Neurontin, like Effexor XR, is often only effective in relatively high doses—sometimes between 800 mg to 1200 mg taken three times per day. Indeed, it is common that patients will present to pain clinics claiming that they "failed" Neurontin, even though they've only increased the dosage to 300 mg three times per day! In my clinic, I don't consider a trial of Neurontin to be a "failure" until a patient has tried at least 600 mg three times per day for a minimum of a week.

If Neurontin either fails or is not tolerated, a host of other medications (mostly anticonvulsants) are now available that show promise in the treatment of neuropathic pain. One such medication is oxcarbazepine (Trileptal), a second-generation Tegretol-like medication that has less troubling side effects than Tegretol. With Trileptal, liver toxicity and bone marrow toxicity are not a concern. However, occasional blood monitoring is required because Trileptal can occasionally induce a state of hyponatremia (low blood sodium level).

Lamictal, Gabitril, Topamax, Zonegran and Keppra are among the newer anticonvulsants that some studies suggest are effective in neuropathic pain. Each of these drugs has a different mechanism of action that may provide advantages for specific patients. For example, Gabitril increases the availability of the neurotransmitter, GABA, which is thought to inhibit abnormal sensory nerve impulses such as those seen in neuropathic pain. Gabitril may prove to be particularly useful in patients who also suffer from anxiety and sleep disorders. Trileptal may be a good choice for those with a prominent shooting component to their pain, as its analogue, Tegretol, is often effective for trigeminal neuralgia, a neuropathic pain syndrome causing shooting pain. Topamax, a drug that is rapidly becoming a drug-of-choice for migraine headache prevention, also appears to be useful in various neuropathic pain conditions. Of course, all of these drugs have potential side effects, but most can be managed when prescribed under the guidance of an experienced clinician. Occasionally, however, some of these drugs can have potentially dangerous side effects; for example, even though it

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rarely occurs, a severe, potentially life-threatening rash has been reported in association with the use of Lamictal, and a form of potentially vision-damaging glaucoma has been associated with Topamax. Consequently, any physician prescribing these medications should be extremely knowledgeable about, and experienced in using, these agents.

Other Medications

Other medications that may play a role in the treatment of neuropathic pain, but are not in the anti-convulsant class, include Zanaflex, Klonopin, Remeron, Ultram, and Mexiletine. Although these drugs must be closely monitored when used in any patient, they can be enormously effective in the treatment of various neuropathic and non-neuropathic chronic pain conditions. Of special note are the drugs Zanaflex, a muscle relaxant, and Ultram, a drug that has opioid (narcotic-like) properties and both serotonin- and norepinephrine-reuptake inhibitor properties. Both drugs have scientific evidence showing efficacy in both neuropathic and non-neuropathic pain.

NSAIDS

This article would not be complete without some mention of the usage of both non-steroidal anti-inflammatory agents (NSAIDS) and opioids in the treatment of various chronic pain states. Second generation NSAIDS, such as Celebrex and Vioxx, are known as COX-2 inhibitors. They are important primarily because they provide essentially the same anti-inflammatory and pain-fighting effects as their predecesors, the non-selective COX inhibitors such as Motrin and Alleve, but are less likely to cause gastrointestinal ulcers than first generation NSAIDS. Because of their possibly better safety profile, they are rapidly becoming the preferred NSAIDS for long-term use.

NSAIDS are generally not considered useful for the treatment of neuropathic pain or centrally-mediated pain (e.g., fibromyalgia) because neither condition is inflammatory-mediated. However, one must remember that all NSAIDS have analgesic (pain-fighting) properties distinct from their anti-inflammatory effects. For this reason, NSAIDS can sometimes be useful in any pain condition—even if neuropathic. In addition, studies show that NSAIDS may enhance the potency of opioids. In my clinical experience, I have found NSAIDS to be most useful for chronic pain when used as combination therapy with other non-NSAID agents such as opioids.

Opioids

Opioid use in the treatment of chronic non-malignant pain still remains controversial in both the medical and lay community. Unfortunately, confusion over issues of addiction, physical dependency, tolerance, and abuse, while important concerns that must be considered, has clouded the fact that opioids can be safely and effectively used to treat many types of chronic pain—both neuropathic and non-neuropathic. It is critical to emphasize the importance of proper patient selection with regard to the usage of opioids for chronic non-malignant pain, because these drugs are not appropriate for every patient. For instance, opioids should be avoided, if possible, in patients with a history of alcoholism or drug addiction, since such patients are more likely to abuse or misuse opioids legitimately prescribed for their pain. Indeed, it is my contention that one of the factors responsible for the recently publicized reports of widespread misuse and abuse of the powerful opioid, Oxycontin, is poor patient selection. There is no doubt that Oxycontin has been unwittingly prescribed for many patients who, had they been appropriately pre-screened, could have been predicted to be high-risk candidates for opioid therapy.

In chronic pain patients who do not have a history of substance abuse, opioids are unlikely to induce a state of psychological addiction. Taking opioids for the treatment of legitimate chronic pain does not, in and of itself, lead to abuse of the drug or to the development of behavioral changes associated with true addiction, such as a pre-occupation with obtaining the drug. Such aberrant behavior is caused by a complicated mix of genetic, environmental, psycho-social, and biological factors, all of which may be present in such a patient even before the first opioid prescription is written. Furthermore, although tolerance and physical dependency often develop when opioids are used legitimately in chronic pain patients, these phenomena are considered to be normal physiological events

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which are generally either inconsequential or easily managed by experienced clinicians.

There are many types of opioids available, including both long- and short-acting forms, as well as oral, trans-dermal, and trans-mucosal formulations. It is beyond the scope of this article to attempt to analyze the merits and negatives of all these opioids. Nevertheless, it is important to note that, like all of the medications discussed above, every prescription for an opioid must be carefully considered and individualized to every patient. Each opioid has specific advantages and disadvantages that may be of particular benefit or harm to any given patient. For instance, many pain specialists feel that methadone may have certain inherent advantages in the treatment of chronic pain. It is often long-acting in many patients; it is generally thought to be less prone to abuse than some other opioids; it seems to induce tolerance (the need for escalating dosages) less quickly than some other opioids; it is inexpensive relative to other long acting opioids; it possesses some NMDA receptor-blocking capability, a characteristic that possibly makes it more useful in chronic pain, in which central sensitization almost invariably occurs; and it possesses both serotonin- and norepinephrine-reuptake inhibition properties. Since central sensitization appears to be a particularly prominent factor in chronic neuropathic pain, methadone may one day prove to be the ideal opioid for the treatment of chronic neuropathic pain, although it has yet to be proven. Methadone may be of particular relevance to the treatment of vulvodynia, a syndrome that, regardless of whether it involves a neuropathic pain component or not, most likely involves a central sensitization component.

Polypharmacy

It is important to understand that it is rare that an opioid, by itself, will adequately treat chronic pain—including vulvodynia. Opioids, though generally the most powerful pain killers available in our treatment arsenal, are not a panacea. Rather, they are most effectively used as part of a pharmacological regimen now commonly referred to as "rational polypharmacy," i.e., using a combination of drugs that work via multiple mechanisms of action to combat chronic pain. Often, such drug combinations harness the power of synergy, a process whereby each drug actually enhances the efficacy of the other. A common synergistic combination is the use of an NSAID with an opioid, the basis behind medications such as Percodan (oxycodone+aspirin) and Vicoprofen (hydrocodone+ibuprofen). Tricyclics, such as amitriptyline, are also commonly used synergistically with opioids, often allowing one to minimize the opioid dose necessary in order to achieve a powerful analgesic effect. Furthermore, combination therapy can sometimes minimize the side effects of each individual medication by offsetting each other's side effects. For instance, the weight gain side effect commonly seen with amitriptyline could be counterbalanced by adding Topamax, a medication that commonly causes weight loss. Another example is the use of Wellbutrin, an antidepressant that sometimes induces alertness and increased energy, to counterbalance the possible sedating effects of opioids. In this manner, a skilled clinician can creatively exploit the positive and negative effects of various medications in order to find the most effective medication regimen with the least number of side effects. ■

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vulvar vestibule; and (3) erythema (redness) of the vulvar vestibule. Although these criteria can be quite useful, they have never been subjected to experimental scrutiny. Bergeron and colleagues tested the reliability of these criteria in a recent study of 146 women with dyspareunia (painful intercourse). Each woman received two separate gynecologic examinations involving vulvar pain ratings, structured interviews, and completion of the McGill-Melzack Pain Questionnaire. Using the Q-tip test for pain sensitivity, pain ratings recorded by both examiners were very similar, but erythema ratings were not significantly correlated. Bergeron concluded that a woman's self-report of pain is a reliable diagnostic indicator of VVS, but that erythema of the vulvar vestibule is not.

Meanwhile, another recent study by Bornstein presented potentially new diagnostic criteria for VVS.

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This study compared vestibular tissue removed from 40 women who underwent surgery for VVS to tissue samples from 7 pain-free controls. Biopsy specimens were analyzed for nerve fiber density and the presence of mast cells (blood cells responsible for allergic reactions). Mast cells secrete chemicals that cause the sensation of itching and burning and can stimulate growth of nerve fibers. Bornstein found a significant increase in both the number of mast cells and nerve fibers in the vestibular tissue of women with VVS. (This study corroborated Bohm-Starke's earlier finding of increased nerve fiber density in the vestibule of VVS patients.) He suggests two new diagnostic criteria for VVS: (1) The presence of eight or more mast cells per HPF (high power field on the microscope) in biopsy specimens from VVS patients, and (2) nerve fiber density in the vulvar vestibule 10 times higher than in the "normal" vestibule.

TREATMENT

In the past few years, several studies have examined the success rate of surgery as a treatment option for VVS. To date, there have been at least 10 published papers on the efficacy of vestibulectomy (surgical removal of the vestibule) in treating the disorder. Bornstein reviewed all vestibulectomy outcome studies between 1981 and 1998; a compilation of the results revealed that 89 percent of VVS patients who underwent vestibulectomy experienced a significant reduction in their pain, and 72 percent reported a complete resolution of their symptoms. Schneider and colleagues reported a similar success rate, and added that 83 percent of women who underwent vestibulectomy said they would recommend it to others.

Outcome studies of electromyographic (EMG) pelvic floor muscle rehabilitation in the treatment of VVS have also been published. McKay reported that 52 percent of VVS patients demonstrated markedly decreased vestibular pain after EMG rehabilitation and that 69 percent resumed sexual activity. According to Sarig's study, 43 percent of patients were able to engage in intercourse without pain after an average of six months of EMG treatment. In the first randomized trial comparing the efficacy of vestibulectomy and EMG treatment in VVS, however, Bergeron reported that the surgery group's success rate was higher than that of either the EMG treatment or cognitive-behavioral therapy groups.

ETIOLOGY

Inflammation

In the past five years, some researchers have discovered differences in the levels of inflammatory substances in the vestibular tissue of VVS patients as compared to asymptomatic controls. Foster found that concentrations of the inflammatory cytokines, IL-1beta and TNF-alpha, were significantly elevated in the vestibule of women with VVS. In another preliminary study, he found significantly higher levels of COX-2 (an enzyme precursor to inflammation) in fibroblasts (a type of cell) within the vestibule of VVS patients. Assuming further research findings corroborate this preliminary data, Foster speculates that COX-induced production of an inflammatory substance known as prostaglandin E may be a factor in the etiology of VVS.

Researchers Witkin and Ledger compared the levels of interferon-alpha in the vestibules of women with VVS and a pain-free control group. Interferon-alpha is an anti-viral substance produced by the body that is believed to possess anti-inflammatory properties. Witkin and Ledger found that women with VVS produce less interferon-alpha than controls and theorized that a deficiency of this substance might contribute to chronic inflammation in VVS.

In another research study, Jeremias, Witkin and Ledger discovered the first genetic link to VVS. Their hypothesis was that susceptibility to developing vulvar vestibulitis is related to genetic variation in immune response genes known to be involved in other inflammatory and immune conditions. This study found that women with VVS are seven times more likely to have the rare (rather than the common) form of the interleukin-1 receptor antagonist gene, a gene that plays a role in terminating inflammation. This line of research is continuing and may establish a genetic basis for the exaggerated inflammatory and immune responses in some VVS patients.

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The results of a recent study by Bohm-Starke, however, did not find active inflammation in the vestibule of VVS patients. Bohm-Starke performed biopsies on 10 women with VVS and 10 pain-free controls and then analyzed the samples for levels of COX-2 and iNOS, enzymes that indicate inflammation. Enzyme activity was low in both groups. Based on this result, Bohm-Starke remarked that the conventional use of topical corticosteroids in VVS patients is unfounded.

Research into potential inflammatory processes in VVS is rapidly evolving and it remains to be seen whether preliminary research findings will be replicated. Because several highly respected researchers are continuing to work in this area, it is likely that the role of inflammatory mechanisms in the etiology of VVS will soon be better understood.

Infection

It has not been determined whether women with vulvodynia have an increased occurrence of yeast infections or if clinicians misinterpret vulvodynia as a yeast infection and inappropriately prescribe antifungal medication. In a recent study, Bornstein and colleagues investigated the assumption that women with VVS have chronic yeast infections. They enrolled 40 women with VVS in this study and assigned them to one of two groups: (1) six-month low-oxalate diet with calcium citrate complement (placebo), and (2) six-month low oxalate diet with calcium citrate complement plus a weekly oral tablet of 150mg fluconazole (treatment). The study found that women in the group treated with fluconazole (Diflucan) did not experience greater pain-relief than women in the placebo group. Bornstein concluded that the prolonged use of antifungal medication is an ineffective treatment in the vestibulitis patient population. He also speculated that there might be a subset of patients who have "complicated" vestibulitis, i.e., VVS as well as co-existent yeast that is resistant to currently available medical treatment.

Central Sensitization

There have been several recent articles suggesting that women with vulvar vestibulitis have increased pain perception throughout their entire bodies, not just in their genitalia. This "central sensitization" theory proposes that VVS is one manifestation of a widespread pain syndrome. Evidence supporting this theory comes from clinicians and self-report surveys that reveal considerable overlap of VVS and other chronic pain conditions such as fibromyalgia, but this hypothesis has yet to be scientifically validated.

Allergic Reaction

Another possible etiology of VVS is supported by recent experimental data. As mentioned earlier, two independent research groups have shown there is a proliferation of nerve fibers in the vestibules of women with VVS. These have been identified as C fibers, known to play a role in the transmission of pain. Bornstein's study found that women with VVS have up to 10 times the number of C fibers as controls. This finding may explain why VVS patients experience severe pain when the vestibule is lightly touched.

Bornstein's study also demonstrated that women with VVS have a large number of mast cells in their vestibular tissue, which may explain the itching and burning experienced by these patients. If you consider the increased number of mast cells, as well as Velangi's finding that that the skin of women with VVS is more sensitive to chemical irritants, it is plausible that VVS may be initiated by an allergic reaction to a chemical irritant. This reaction, possibly to topical antifungal agents used to treat suspected candidiasis, may cause mast cells to migrate to the vestibule. If the irritation persists, the mast cells then secrete hormones causing nerve fibers to proliferate. This "allergic reaction" hypothesis may explain why up to 80 percent of women with VVS report an acute onset of symptoms, i.e., burning and itching. The initial reaction then progresses to severe pain on touch because of the proliferation of nerve fibers. Clearly, research studies are required to test the validity of this hypothesis.

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Recent Findings

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SUMMARY

In conclusion, in the past few years scientists and health care providers have made great progress in understanding and treating VVS. Although there is much more to learn, we are closer today to understanding the cause or causes of VVS than we were five years ago. Hopefully, this ongoing research will soon lead to the development of more effective treatment for the women who suffer from this difficult and complicated condition.

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