Third Gynecologic Pain Research Virtual Meeting

Gynecologic Health and Disease Branch (GHDB)

Division of Extramural Research (DER)

Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)

National Institutes of Health (NIH)

June 13, 2024

1 p.m.–5 p.m.

Welcome and Opening Remarks

Candace Tingen, Ph.D., Chief, GHDB, NICHD

Alison Cernich, Ph.D., ABPP-CN, Deputy Director, NICHD

Dr. Tingen welcomed the attendees and thanked the planning committee for creating a packed agenda for the meeting.

Dr. Cernich said that gynecologic pain affects an estimated 26% of people worldwide—often severely enough to affect their quality of life, though society tends to normalize it. Delays in diagnoses spell years without treatment and impair research.

NICHD's mission is to lead research and training to understand human development, improve reproductive health, enhance the lives of children and adolescents—and optimize abilities for all. One aspirational goal in NICHD's Strategic Plan is the diagnosis, prevention, and treatment of endometriosis, which affects about 10% of U.S. women and can cause chronic pain, infertility, and higher risk of some cancers. Gynecologic pain is a priority for NICHD, and the institute conducts and supports research that improves the understanding of mechanisms, diagnosis, and treatment of gynecologic pain and associated conditions, such as endometriosis, uterine fibroids, and vulvodynia. NICHD also sponsors the Pelvic Floor Disorders Network.

Recently, NICHD-funded researchers at the University of California, San Francisco found that fenoprofen reduced pain and inflammation in a rodent model of endometriosis. NICHD held a panel discussion on endometriosis in conjuction with a screening of the 2023 endometriosis documentary *Below the Belt*. NICHD has launched the Advancing Cures and Therapies and ending ENDOmetriosis diagnostic delays (ACT ENDO) initiative, with information on funding opportunities coming soon.

Overview of GHDB and Gynecologic Pain Program

Helena Ahn, Ph.D., Program Officer, GHDB, NICHD

One of the five themes of the NICHD Strategic Plan 2020 is promotion of gynecological, andrological, and reproductive health. GHDB aims to improve women's reproductive health by guiding and supporting gynecologic research and career development programs. One of the program priorities for GHDB is to understand mechanisms of gynecological pain.

In GHDB, Dr. Candace Tingen oversees the endometriosis, adenomyosis, uterine fibroid, and menstruation and endometrium portfolios. Donna Mazloomdoost, M.D., GHDB medical officer, oversees the pelvic floor disorders, obstetric fistula, and female genital cutting portfolios. Dr. Helena Ahn oversees the gynecologic pain portfolio.

NICHD has announced ACT ENDO, which will accept applications to develop, advance, or validate new devices, biomarkers, or methods or to repurpose existing devices for noninvasive diagnosis of endometriosis. GHDB supports two related funding opportunities titled Understanding Chronic Conditions Understudied Among Women. The branch is also participating in funding opportunities for the NIH Helping to End Addiction Long-term® Initiative (NIH HEAL Initiative®). GHDB manages the Building Interdisciplinary Research Careers in Women's Health (BIRCWH) K12 program.

This is the third annual Gynecologic Pain Research Virtual Meeting. It will cover the topics of endometriosis-associated pain, menstrual pain, vulvar pain, gynecologic pain management and treatment, and U.S. Food and Drug Administration (FDA) regulations and guidelines.

Session I

Moderator: Candace Tingen, Ph.D., Chief, GHDB, NICHD

Insights Into Endometriosis: Unraveling the Role of Risk and Resilience in Pelvic Pain

Emily Bartley, Ph.D., Assistant Professor, Pain Research and Intervention Center of Excellence, University of Florida

Dr. Bartley's team is exploring the vulnerability and protective factors implicated in endometriosis disease burden. Endometriosis is an estrogen-dependent disease in which endometrial-type tissue is outside the uterus. It affects more than 10% of women, including more than four million in the United States alone. It causes infertility and pain, the latter during menses and sexual intercourse, sometimes in the bowel or bladder. Many women with endometriosis have generalized or noncyclic pelvic pain. Pain is one of the main reasons why women seek healthcare.

Diagnosis may take more than a decade from the onset of symptoms. Many women with endometriosis report depression, related not only to the unpredictable and severe symptoms but also to having their experience repeatedly dismissed by health care providers.

In a survey of 100 people with pelvic pain, many of whom had endometriosis, about 80% reported that pelvic pain had a moderate to high impact on their lives. Therapies generally start with suppression of estrogen levels through hormonal contraceptives; more than half the

participants reported persistent pain after the end of such therapy. Pain also comes back for many people after surgery.

Symptom severity does not correlate well with the severity of endometriosis. Women with mild endometriosis, for example, may have a high degree of pain. Heterogeneity of disease and symptoms may help explain inconsistent therapy results.

Dr. Bartley's team has studied how various demographic, pain quality, behavioral, and psychological factors relate to pelvic pain. The participants who reported being most affected by pelvic pain tended to have a higher body mass index, greater symptoms of central sensitization, higher rates of sleep disturbance, more negative psychological functioning (e.g., anxiety), and lower levels of protective resources (e.g., optimism).

Endometriosis has high co-prevalence with other chronic overlapping pain conditions (COPCs), which are 10 disorders such as chronic fatigue syndrome and fibromyalgia with poorly understood pathophysiologies. These conditions have a high degree of comorbidity. Dr. Bartley's team found that women with more COPCs reported more central sensitization, which may play a role in endometriosis. In a sample of 525 women with chronic pelvic pain, 25% of whom had endometriosis, those with endometriosis reported more severe pain, interference from pain, and impact of pain. They had more COPCs, particularly chronic fatigue syndrome, fibromyalgia, and temporomandibular disorder, and many had three or more COPCs.

The etiology of endometriosis is multifactorial, including peripheral modulators and central mechanisms that augment pain. In recent years, researchers have been working to identify endometriosis subgroups based on patterns of pain presentation and comorbidities.

Phenotyping shows promise, but much is still unknown. A current R21 study by Dr. Bartley's team explores phenotypic predictors of pelvic pain impact and physical functioning in women suspected of having endometriosis and undergoing conservative medical management. The study follows the women for six months to look for factors that cluster together, such as demographics, health and pain comorbidities, sleep quality, and various psychological risk and resilience factors. In early findings, patterns of change in pain over time have shown dramatic individual variation.

Endometriosis is very heterogeneous in both presentation and in treatment efficacy. Factors other than peripheral damage may contribute to the generation of endometriosis pain. Identifying some of the characteristics that predict individual variability may help lead to individualized and improved patient care.

Discussion

Dr. Tingen asked whether diagnosis changes the experience of pain for endometriosis. Dr. Bartley said that not knowing what one has is detrimental to psychological and physical health and likely affects the experience of pain. Receiving a diagnosis can be healing.

Dr. Tingen asked about resilience factors. Dr. Bartley said that her team has found psychosocial factors that are associated with lower levels of disability for women with pelvic pain. Her team has looked at the Brief Resilience Scale and the Pain Resilience Scale. Factors such as poor sleep practices have a negative impact.

An attendee mentioned that their study found no difference based on race.

Development of Anti-Inflammatory Nanodrug for Endometriosis Treatment

Jae-Wook Jeong, Ph.D., Professor, Department of Obstetrics, Gynecology and Women's Health, University of Missouri

Women with endometriosis have higher levels of pro-inflammatory mediators in peritoneal fluid, ectopic lesions, and eutopic endometrium. Nonsteroidal anti-inflammatory drugs (NSAIDs) can reduce pain from endometriosis. Dr. Jeong's team is interested in understanding which molecules are involved in endometriosis pathogenesis.

The molecule signal transducer and activator of transcription 3 (STAT3) is localized in the cytoplasm until it is activated by phosphorylation. Various cytokines activate STAT3. After activation, it moves to the nucleus. Phosphorylated STAT3 (pSTAT3) is connected to angiogenesis, immunosuppression, inflammation, and chronic pain. Aberrant activation of STAT3 signaling in endometriosis has been found in the human endometrium. In baboon and mouse models, pSTAT3 level increases after induction of endometriosis.

Dr. Jeong's team hypothesizes that pSTAT3 signaling plays an important role in immunosuppression, inflammation, and chronic pain in endometriosis, and could be a target for therapeutics.

Dr. Jeong's team developed a mouse model with a uterine-specific reporter system. Bioluminescence makes it possible to detect uterine tissue in the live animal. Endometriosis is induced by injecting uterine tissue into the peritoneum. This model enables the study of endometriosis-linked infertility and pain.

The mouse model of endometriosis responds to hormones as do humans. In the mouse, endometriosis can cause infertility, with implantation failure and decidualization defect.

Progress in treating endometriosis has been slowed by the lack of an animal model that fully replicates human pathophysiological characteristics. Pain in animals is usually measured by reflex and nonreflex tests. Reflex tests apply a noxious stimulus and evaluate hypersensitivity, but do not assess the emotional component. Nonreflex tests include burrowing, marble burying, and nesting tests. These nonreflex tests suggest that mice with endometriosis are experiencing more pain; for example, in the marble burying tests, mice with endometriosis are less effective at hiding marbles in their bedding.

Tofacitinib is an FDA-approved STAT3 inhibitor used to treat arthritis, colitis, and Crohn's disease. It reduced the number of endometriotis lesions in mice. However, it also results in implantation failure. Dr. Jeong's team hypothesized that using nanoparticles would reduce such systemic effects. Drug delivery by nanoparticles reduces off-target toxicity. In mice, theranostic (therapeutic and diagnostic) nanoceria nanoparticles were found to reduce lesions via systemic injection without impairing implantation.

Discussion

Dr. Tingen thanked Dr. Jeong for explaining a mouse model for endometriosis in lay terms. Dr. Jeong said that developing the model was difficult. He added that even mice showed individual differences. Monitoring behavior in the live animal, along with testing behavior, was important.

Dr. Tingen said that being able to see lesions would be very helpful for diagnosis. Dr. Jeong said that this is an advantage of the nanoparticle. He noted that this has been well applied in cancer. Dr. Tingen observed that endometriosis resembles cancer in certain ways and thus might be approached with some of the same tools as cancer biology.

How Does Menstrual Pain Become Chronic Pain?: The Role of Central Sensitization in Primary Dysmenorrhea

Laura Payne, Ph.D., Assistant Professor, Department of Psychiatry, Harvard Medical School

Primary dysmenorrhea is menstrual pain without any identified tissue pathology. Menstrual pain affects up to 90% of reproductive-age girls and women, and 20% to 25% experience severe, disabling symptoms, sometimes skipping important activities. Menstrual pain can affect girls' ability to concentrate and function in school.

Many cross-sectional studies have found a link between menstrual pain and chronic pain. A meta-analysis by Li et al. (2020) found a strong link between menstrual pain and a chronic pain condition. Hardi et al. (2014) studied 100 women with chronic pelvic pain. All had previously had dysmenorrhea; for more than half, chronic pelvic pain developed within 12 years of the onset of dysmenorrhea. Li et al. (2021) studied 841 adult women from a national longitudinal study. Dysmenorrhea at baseline was associated with a 41% greater risk of developing chronic pain 10 years later.

Central sensitization refers to long-lasting changes in the central nervous system that affect how pain is processed and experienced.

Many researchers have focused on quantitative sensory testing, which involves using different painful stimuli and measuring reactions. Dr. Payne's team reviewed experimental pain findings in women with primary dysmenorrhea from 1944 to 2017. In general, these women experienced more pain sensitivity and less pain tolerance compared with healthy controls, across all phases of the menstrual cycle.

In one study, Dr. Payne's team tested cold water pain tolerance in adolescent girls. Those with primary dysmenorrhea exhibited lower pain tolerance. The researchers also looked at a different type of testing, a conditioned pain modulation paradigm, which showed no group differences.

A multisensory sensitivity model includes sensitivity to light, sound, smell, taste, touch, and allergies. Kmiecik et al. (2023) studied 200 young women with menstrual pain, bladder pain syndrome, or nonpelvic chronic pain and found that a composite measure called multimodal hypersensitivity, which included audio and visual senstivity, was the best predictor of pelvic pain four years later.

In an ongoing study, Dr. Payne's team follows 141 teenage girls, none of whom have chronic pain, with a range of menstrual pain levels. Girls with major psychiatric issues were also excluded because the study has a functional magnetic resonance imaging (fMRI) component. The team used the Sensory Hypersensitivity Scale, a menstrual pain severity trajectory, and a pain "widespreadness" trajectory to assess the subjects at baseline and monthly for 12 months. Pain widespreadness is a proxy for chronic pain. Of these girls, 80 showed no increase in

menstrual pain; their number of body pain locations decreased. But if they had high sensory hypersensitivity, they still had more body pain locations. The girls with an increase in menstrual pain and high sensory sensitivity reported significantly more body pain locations over 12 months, and therefore seemed to be at high risk for chronic pain.

Pain sensitivity is just one aspect of central sensitization; focusing on this may have limited identification of other risk factors for the transition to chronic pain. People with multisensory sensitivity may be at greater risk for chronic pain. More longitudinal studies of menstrual pain are needed. This new understanding of the role of sensitivty may enable new treatment approaches to prevent chronification of pain.

Discussion

Dr. Tingen expressed surprise at the importance of sensitivity to light and sound. She wondered whether anyone was using multimodal hypersensitivity for assessment in the clinic. Dr. Payne said she did not believe so. She said that the narrow focus of pain research has been a barrier. Her lab is considering alterations in the gut microbiome as a possible mechanism. There has been some research on using behavioral strategies to reduce widespread sensory sensitivity.

Summary of a Recent Vulvodynia Therapeutics Research Summit

Andrew Goldstein, M.D., FACOG, IF, Director, The Centers for Vulvovaginal Disorders

The field of vulvodynia is less advanced than endometriosis, with respect to developing new therapies. The goal of the Vulvodynia Therapeutics Research Summit, held in April 2024, was to advance treatment of vulvodynia. The summit grew from an effort to develop and publish a vulvodynia nomenclature. Vulvodynia is a multifactorial set of disease states. Basic science research has made progress on finding pathways to target. The goals of the summit were to:

- Identify novel medications, compounds, and treatments for vulvodynia based on current understanding of pathophysiology.
- Develop a consensus on three or more of the most promising and feasible ideas.
- Produce a white paper or similar document that could be presented to NICHD and other potential funding organizations.

The attendees identified 15 potential therapeutics. After the summit, attendees ranked the most promising candidates. The top choices were ketotifen, resiniferatoxin, and maresin 1.

Ketotifen fumarate is an eyedrop used mainly for allergies. In an animal model of vulvodynia, zymosan is injected into the vulvas of rats, causing mechanical sensitivity and increases in mast cells and nociceptors in the vestibule. In studies presented at that symposium by Jacob Bornstein, M.D., animals were injected with ketotifen before the zymosan challenge. This reduced inflammatory cytokines and accumulation of mast cells. It reduced pain and pain-related anxiety in the rats. Ketotifen also suppressed neuroinflammation, neural activity, and gene expression related to inflammation and pain receptors in the spinal cord. This suggests that ketotifen may be able to reduce local inflammation and prevent central sensitization by preventing increased inflammation in the central nervous system.

Research on resiniferatoxin was presented by Michael Iadarola, Ph.D., of NIH. Resiniferatoxin is a transient receptor potential vanilloid 1 (TRPV1) agonist that causes calcium overload, leading

to cytotoxicity of neurons. It causes highly selective chemo-axotomy. Resiniferatoxin is an analog of capsaicin but is much more potent. Capsaicin has been used for neuroproliferative vestibulodynia. It is currently being tested in Morton's neuroma. A Phase I study is proposed for resiniferatoxin in neuroproliferative vestibulodynia.

Research on maresin 1 was presented by Megan Falsetta, Ph.D., of the University of Rochester. Maresin 1 is a specialized pro-resolving mediator, a lipid mediator that promotes the resolution of inflammation. Studies have shown that vestibulodynia involves significant inflammation. Decreasing the inflammation could help prevent the onset of vulvodynia or potentially treat the condition. In a mouse model and cells from women with vestibulodynia, maresin 1 reduced inflammatory mediators and pain.

Discussion

Dr. Tingen asked about next steps and said that NIH would be interested in applications in this area. Dr. Goldstein said that many researchers have not applied for NIH funding. He noted that maresin 1 and resiniferatoxin are moving toward Phase I trials, and ketotifen may also. Anyone could take up research on these compounds.

An attendee asked about the pain profile of new therapeutics. Dr. Goldstein said resiniferatoxin would be administered only after local analgesia.

Another attendee asked how the therapeutics might measure against the current standard of care, such as topical estrogen. Dr. Goldstein said that the problem with vulvodynia is that it is a large group of disorders. Topical hormones may be beneficial in some cases but are not likely to be useful in vulvodynia that is inflammatory or neuroproliferative. The goal of the vulvodynia nomenclature is to define subcategories of vulvodynia, including underlying histopathology. Previous large-scale studies in gabapentin and desipramine that NIH funded failed to show benefit, but that may have been because the correct participants were not selected.

Barriers to Care: Vulvovaginal Pain Patient Perspectives

Noa Fleischacker, Executive Director, and Keena Batti, Los Angeles Chapter Co-Coordinator and Campaign Co-Lead, Tight Lipped

Ms. Fleischacker introduced Tight Lipped, a grassroots advocacy organization that represents people with chronic vulvar, vaginal, and pelvic pain conditions. Many people with vulvovaginal pain have trouble getting a diagnosis and finding effective treatment. Ms. Fleischacker said that she has personal experience with pelvic floor dysfunction and vulvodynia. She went to her gynecologist with pain any time vaginal insertion was attempted; her gynecologist thought this was based on anxiety and offered only the solution of performing a pap smear under general anesthesia.

Tight Lipped began as a storytelling podcast. The organizers heard from many people who had experienced the same struggles and obstacles to care. The organization works with patients and medical providers toward a future in which people with vulvovaginal and pelvic pain can lead full lives, free of stigma and able to access the care they need.

Across the United States, the organization has active chapters, run by volunteers with pelvic dysfunction and pain. Members have a variety of conditions, including vulvodynia, vestibulodynia, and lichen sclerosus.

Vulvovaginal pain conditions are common, affecting 10% to 28% of women in the United States at some point in their lifetime. People who are nonbinary and transgender can have these conditions. Tight Lipped has a medical advisory board of experts in sexual medicine, pelvic floor issues, and more.

Ms. Batti shared her story: She started taking birth control pills at age 19, and throughout her 20s had urinary tract infections (UTIs). At 28 she had a UTI that would not go away and led to excruciating pain, including burning, stinging, and itching in her vulva. She could not use tampons, wear pants, or have sexual intercourse. She was diagnosed with hormonally mediated vestibulodynia and was angry because she had not been informed that this was a potential side effect of hormonal birth control.

A urologist prescribed topical hormone medications that were not covered by insurance and cost nearly $250 out of pocket. The problem did not respond to the medications as expected, and Ms. Batti was diagnosed with a separate autoimmune condition. Doctors did not have answers for her, even though autoimmune conditions affect many people. She had expensive off-label procedures. Decision making was stressful in part because of the financial impact on her family. The procedures were effective, but the whole experience was frustrating, expensive, and anxiety-inducing.

Ms. Batti now knows that there are genetic markers for people who are prone to developing vestibulodynia after taking oral contraceptives. With funding, there could be a test for people to take before starting birth control pills. There is a misconception that vestibulodynia is a rare diagnosis; in reality, no one knows how many people it affects. There are no data that can be used to persuade insurance companies to cover procedures.

Ms. Fleischacker said that she hears regularly from patients like Ms. Batti, who share their experiences with an expensive trial-and-error approach to treatment.

Barriers to care include stigma, which makes it difficult to discuss chronic vulvovaginal and pelvic pain with others; a lack of education and medical knowledge, which make it difficult to find a provider who can diagnose and treat the conditions; a lack of research on treatments and treatment effectiveness; and a lack of insurance coverage. Chronic pelvic pain care can cost as much as $20,000 a year.

A letter to the White House Initiative on Women's Health Research, authored by Tight Lipped, received 835 patient signatures. People wrote moving testimonials about why it is important to them to have more research and investment in these conditions.

Discussion

Dr. Tingen said that it is helpful for attendees to hear what people feel. She asked whether people could contact Tight Lipped with questions or for help finding clinicians. Ms. Fleischacker said that Tight Lipped has a list of clinicians.

The National Vulvodynia Association

Susan Kellogg Spadt, Ph.D., Director, Female Sexual Medicine, the Center for Pelvic Medicine, Academic Urology of Pennsylvania

The National Vulvodynia Association (NVA) was formed in 1994, when less was known about chronic vulvar pain. The NVA was created to help improve the health and quality of life of women suffering from chronic vulvar pain. The group's mission is to provide up-to-date treatment and research information so that patients can make informed decisions about their health care, maintain a nationwide referral list of health care providers who treat vulvodynia, and promote and fund research on the pathophysiology and treatment of this condition.

Under the International Society for the Study of Vulvovaginal Disease (ISSVD) classification, vulvodynia is vulvar pain of at least 3 months' duration, without a clearly identifiable cause, which may have potential associated factors. It can be generalized or localized, provoked or spontaneous, primary or secondary, intermittent or constant, and immediate or delayed.

The lifetime prevalence of vulvodynia is estimated at 8% to 28% among women of reproductive age. The most common subtype is provoked vestibulodynia, which is pain upon contact to the vulvar vestibule, with a prevalence of 8%. Despite high prevalence of vulvodynia, only 60% of affected women seek treatment, and only about 50% of those women receive a formal diagnosis.

Vulvodynia limits daily life, including activities such as sexual intercourse and physical exercise. Some women resign from their jobs because they cannot sit for an extended time. Applying for disability is difficult and often results in denial.

Patient services that the NVA offers include an online patient tutorial, four online educational booklets, referral lists to help patients find providers with expertise in diagnosis and treatment of chronic vulvar pain, and support contacts who can answer questions, provide local resources, and offer emotional support.

Health care provider services that the NVA offers include an online tutorial on diagnosis and treatment, quarterly research abstracts, promotion of recruitment for clinical studies, grants to start vulvar pain clinics, and research grants up to $100,000.

The NVA has awarded almost $2 million in pilot research grants. NVA grant recipients have used their pilot data to obtain large grants from NIH and the Canadian Institutes of Health Research. In addition, the NVA offers a career development award to junior faculty. The NVA's pain clinic award has supported the opening of 11 clinics, all of which are still operating. International applications are also welcomed.

The NVA offers newsletters with research abstracts that are helpful for clinicians and people suffering with vulvodynia, advice about sexual intimacy, and personal stories.

The NVA funded the National Vulvodynia Registry from 2009 to 2014. The median patient age was 29; 90% of patients were diagnosed with vestibulodynia and 90% with pelvic floor dysfunction. The most common treatments were topical lidocaine and estradiol, pelvic floor muscle therapy, and a tricyclic antidepressant or anticonvulsant like gabapentin. After 6 months

of treatment, most patients reported less pain and distress but no improvement in sexual function.

To fill a need for continuing medical education in vulvodynia, the NVA developed a self-guided online tutorial. The material was written by volunteer vulvodynia experts. Today almost 50,000 health care providers have viewed the tutorial, and 22,000 have successfully completed the post-test.

The NVA works with support leaders in the United States and Canada. It also maintains Facebook and Instagram channels. Being part of a community gives patients hope and helps them get the care they need. The NVA helped support the research summit that Dr. Goldstein described earlier.

Session II

Moderator: Helena Ahn, Ph.D., Program Officer, GHDB, NICHD

Managing Pelvic Pain and Healing via Humancentric, Harmonic, and Holistic Techniques

Zachary Lyon, Chief Executive Officer, H3Pelvic Therapy Systems, Inc.

H3Pelvic Therapy Systems is trying to help people with chronic pelvic pain conditions by using controlled thermal neuromodulation therapy (TNT). The side effects of medication for pelvic pain can be problematic. In an online survey of people with pelvic pain, nearly half said their pain was constant. They reported that the biggest challenge was that the pain would not go away, followed by a lack of understanding on the part of doctors. Nearly 75% reported spending $500 or more in the past year seeking relief for their pelvic pain. The company is now focusing on interstitial cystitis.

TNT works well for some conditions. Inflammation drives pain, and cooling can reduce inflammation. Cooling affects the channels that allow flooding neurons to turn off pain signals to the brain.

The company's product uses a tampon-sized probe to introduce cooling thermal energy into the vaginal lumen, transmitting it to the pelvic region. The company is working with researchers at Duke University to understand how deep the energy is reaching into pelvic tissue. The probe is silver-plated and biocompatible. It rapidly delivers passive thermal energy.

The company is using a swine model to test the device. The pig probe is different from the human probe because the bladder is farther from the opening of the vagina. Sensors were placed inside swine to measure thermal energy.

A thermal neuromodulation delivery device would be used at home. The current focus is the EOS probe. The device will combine a probe and a seat. Twenty-one pilot customers have tested a prototype and said that it helped them.

The company, which was formed in 2020, has applied for patents. In 2022, it had two rejections from NIH, but in 2023, H3Pelvic Therapy Systems received a Phase I Small Business Innovation Research (SBIR) award for $385,000 from NICHD.

It is not clear whether this system has predicates, and the company would like to move the product into the commercial space as soon as possible. H3Pelvic Therapy Systems believes it is

a nonsignificant risk device. The company hopes that this will create a new standard of care for treating pelvic pain.

Discussion

An audience member asked what the device is made of. Mr. Lyon said that the seat is made from a material known to be medically biocompatible. The membrane is latex, but there will be other options for people with a latex allergy. The probe is a silver-plated biocompatible material.

A Device to Treat High-Tone Pelvic Floor Dysfunction in Women

Jose Bohorquez, Ph.D., President, Bold Type, LLC

The company's research is funded with a Phase I SBIR grant from NICHD. The inventor of the company's device is Erin Carey, M.D., MSCR, of the University of North Carolina at Chapel Hill. The device is designed to treat pelvic floor dysfunction, which may include pelvic pain, constipation, or urinary incontinence caused by the muscles in the pelvic floor. They are focusing primarily on conditions in which the muscles are too tight.

As many as 37 million women in the United States suffer from pelvic floor dysfunction. About 10 million initiate pelvic floor physical therapy. Impact can include limits on physical activity, trouble with sleep, relationship problems, and depression/anxiety.

The first-line therapy is pelvic floor physical therapy. A session might include patient education, pelvic floor exercises, manual therapy, and soft tissue manipulation with mechanical wands. Less than a third of the women who are prescribed pelvic floor physical therapy complete it. Reasons include financial constraints, time constraints, travel issues, and fear. Barriers to doing the therapy at home include uncertainty about how to perform the therapy correctly.

The company is developing a "SmartWand system"—a mechanical wand with sensors inside that communicates with an app on the patient's device via Bluetooth. The data can go to the cloud. The company is developing a web application that the physical therapist can use to interface with the patient. This will support the physical therapist in treating patients. The idea is that the physical therapist sets up the device for the patient, then the patient does the exercises and therapy at home, with the app tracking the work. The physical therapist reprograms the device at the next visit.

Patients are normally prescribed physical therapy as 12 weekly visits in person, plus three days a week of exercises at home. Only about half of the patients make it to the second session. The SmartWand could reduce the in-person visits to four, with the other eight performed through telehealth. This will likely be more comfortable and convenient for the patient. The app could also provide educational content.

The wand has sensors inside. The section that is inserted has touch sensors that track how deeply the wand is inserted, gauges that accurately measure the force being applied, and an accelerator to measure rotation of the wand as it is inserted. A demo version of the app is currently being used in clinical research. The app guides the patient and gives feedback on whether they have the wand in the right place and are using enough pressure. A counter shows them how long to hold it in place.

Discussion

A participant asked about a connection between Lyme disease and vulvodynia. Dr. Bohorquez noted that he has an engineering degree and is not a medical doctor. However, the device may be helpful in any case in which myofascial physical therapy would be helpful.

A participant asked how the user will hold the phone and wand at the same time. Dr. Bohorquez said that the person will likely need a phone stand. It is possible to operate the wand with one hand, but it may be more comfortable with two hands.

Dr. Goldstein asked about targeting the puborectalis and transverse perineal muscles. Dr. Bohorquez said that this device can be used on any pelvic floor muscles accessible through the vagina.

Mucoadhesive Film for the Treatment of Vestibulodynia

S. Rahima Benhabbour, Ph.D., M.Sc., Founder and Director, AnelleO, Inc., and Associate Professor, Joint Biomedical Engineering Department, University of North Carolina at Chapel Hill and North Carolina State University

Vulvodynia is an idiopathic pain disorder characterized by pain, burning, and itching. In the United States alone, about 12 million women are diagnosed with vulvodynia, 62% of which have limited intercourse because of pain, and only 58% receive treatment. Dr. Benhabbour's group is working to develop a new treatment modality for vulvodynia.

Vulvodynia is the most common cause of sexual pain. The first line of defense is topical lidocaine ointment, which has short-lived efficacy. An ointment is messy, hard to apply, and can leak, leading to inadequate dosing and limited efficacy. Because of this, patients may not continue the treatment. The second line treatment is systemic medications or cognitive behavioral therapy. The third line is vestibulectomy, which is surgery. There is no FDA-approved product for treatment of vulvodynia to date; all products are used off-label.

Dr. Carey brought the problem with lidocaine delivery to Dr. Benhabbour because her group specializes in drug delivery. Their goal is to develop mucoadhesive thin film that would be localized and specific, to deliver lidocaine or other drugs to the area of inflammation. It could be applied and removed or left in place for longer-acting delivery. The films have the shape of the area of vulvar inflammation to cover the area.

The group held focus groups with patients presented with an early prototype based on anatomical measurements, and the patients were not able to touch the product; most focus groups were virtual. The results were published, and the patients gave both positive and negative feedback. Those who had been using lidocaine and had not seen a benefit were skeptical but willing to try a film. Most of the women wanted multiple size options. They felt that the film shape would make it easy to apply, and preferred a thin, flexible film without sharp edges. They wanted the film to be portable, and to be applied and then removed. Focus group results suggest that the film would be acceptable to women with vulvodynia. It is a platform and could be used for other drugs.

The company is using a fabrication method that can easily be utilized for a good laboratory practice (GLP) and good manufacturing practice (GMP) product. They have identified a contract

research organization (CRO) to scale the process under GMP manufacturing and will be testing three prototypes. The manufacturing is a simple three-step solvent casting method.

The team strategically picked materials that are already approved by FDA for film use. Changing the amount of lidocaine or the formulation properties changes the duration. The release kinetics can be changed to alter delivery.

The team selected two formulations with appropriate release kinetics and tested them in a mouse model, compared with the 5% lidocaine ointment that is prescribed to women. They found that exposure in the target tissue is much higher than the systemic exposure, as hoped. In addition, the amount of drug in the vaginal tissues was much higher with vaginal film. The team also carried out safety studies in mice. They did not find chronic or gross toxicity locally or systemically.

Next the team worked to develop a unidirectional film, which will deliver the drug only toward the vulvar tissue and not to the other side, with a backing layer that would not affect the properties of the main film. In addition, the films are stable long-term, and the drug's characteristics and release kinetics do not change after six months. The work is currently funded by an NICHD Phase II SBIR grant.

FDA Regulations and Guidelines: FDA Review of Gynecological and Surgical Devices

Reginald Avery, Ph.D., Team Lead, Gynecological and Surgical Devices Team, Center for Devices and Radiological Health (CDRH), FDA

FDA is a consumer protection and regulatory agency with the mission to protect and promote the public health; CDRH is one of the centers of FDA. The Office of Product Evaluation and Quality is responsible for the total product life cycle review of medical devices. This includes premarket review and activities after devices are on the market. Dr. Avery's team is in one of the offices of health technologies. This team's work includes male and female urology devices, obstetric and gynecological devices, surgical tools, and incontinence devices.

Dr. Avery focused on premarket activities. Cross-disciplinary review teams work to make sure there are safe and effective devices on the market. A medical device has a technical definition in the Food, Drug, and Cosmetic Act. Part of that is that a device is intended for use in the diagnosis of disease or other conditions; or in the cure, mitigation, treatment, or prevention of disease; or is intended to affect the structure or any function of the body and does not work through chemical action. This helps distinguish devices from drugs or biologics. Medical devices also include some software functions, such as mobile apps.

Medical devices are classified as Class I, II, or III based on risk level and the regulatory controls needed to provide a reasonable assurance of safety and effectiveness. Class I devices are low- to moderate-risk and need only general controls to provide a reasonable assurance of safety and effectiveness. Examples of general controls include registration and listing requirements.

Class II devices are moderate- to high-risk. General and special controls are required. Special controls are usually device-specific requirements. These may include nonclinical testing requirements and labeling requirements. They typically require a 510(k) to be authorized for marketing.

Class III devices require general controls and premarket approval (PMA).

The Pre-Submission Program is a commonly used approach for sponsors, researchers, investigators, and manufacturers to communicate with FDA review teams to help facilitate bringing a device to market. Through this program, they can receive feedback on regulatory strategy, animal testing protocols, and other aspects of device-making. Sponsors can submit pre-submissions at any time before they submit a marketing application, to help ensure that they are aligned with FDA.

An investigational device exemption (IDE) may be required if a clinical study is being conducted. FDA will determine whether the device can be used safely in the study based on submitted data. FDA will also provide recommendations to support a future marketing application, such as a more appropriate primary endpoint or a recommendation for additional nonclinical testing.

The most common marketing application types for gynecological devices are 510(k), De Novo, and PMA pathways. All are subject to a user fee.

- The most common pathway for gynecological devices is the 510(k). The regulatory framework for a 510(k) is to demonstrate that the device is as safe and effective as a legally marketed predicate device, or that a device is substantially equivalent to a predicate device.
- De Novos are another type of regulatory system that allows FDA to classify low- to moderate-risk devices without an appropriate legally marketed predicate. The review team confirms that there is no predicate as part of the process. The regulatory framework is to determine whether general controls and special controls are enough to provide a reasonable assurance of safety and effectiveness.
- PMAs are the most stringent type of marketing application. This includes high-risk devices, such as life-sustaining devices. There are no predicate devices, so the sponsor has to demonstrate independently that there is a reasonable assurance of safety and effectiveness.

Another application type is the Breakthrough Device designation, which was established by the 21st Century Cures Act. Criteria include the device's ability to provide a more effective treatment or diagnosis of life-threatening or irreversibly debilitating human diseases or conditions.

FDA activities and manufacturer responsibilities continue after a device receives marketing authorization. Sponsors must meet regulatory requirements, including Medical Device Reporting, for all devices. FDA can carry out inspections and take enforcement actions if companies are not in compliance.

Understanding the IND Process

Margaret Kober, R.Ph., M.P.A., Chief, Office of Regulatory Operations, Center for Drug Evaluation and Research (CDER), FDA

Devices and drugs are regulated differently. Ms. Kober, who is involved in review of applications to the Division of Urology, Obstetrics, and Gynecology, gave a brief overview of drug regulation.

IND stands for *investigational new drug*. A new drug is one that either has not been approved by FDA or is an approved drug being used for a new indication, if the new use would introduce new risks or make the known risks less acceptable. The IND application requirements are laid out in 21 CFR 312.23. They include a cover letter, which should be well written; various forms; and an Investigator's Brochure, if there are multiple investigators.

The IND application includes nonclinical data to support the drug's use in human trials and a section on chemistry, manufacturing, and controls that shows the drug can be manufactured accurately and safely. The sponsor should also include the clinical protocol, including supporting data, such as data from outside the United States and pharmacokinetic data, and details on how the safety of participants will be ensured.

An IND that is not being conducted for commercial purposes can be submitted on paper. The IND application can also be submitted through an electronic portal. Submission via the electronic portal is required for a commercial IND. Email submissions are never an option.

When an IND is submitted, FDA assembles a review team including regulatory, clinical, chemistry, and other expertise. A combination product—with both a drug and device and a primary mode of action that is chemical—is reviewed primarily by CDER, but the team will consult with colleagues with expertise in devices. FDA has 30 days from receipt of the application to determine whether the study is reasonably safe to proceed or whether it will be placed on clinical hold, which means that the study cannot be conducted in the United States. FDA does not approve INDs; it allows them to proceed. If the sponsor does not hear back from FDA, the study can proceed. Sometimes FDA does ask the sponsor to delay starting the study until FDA has had time to finish. FDA can often offer advice on how to reach study objectives more efficiently.

IND amendments include both protocol amendments (such as a new protocol, a change in protocol, or addition of a new investigator) and information amendments (such as new information from foreign studies or on clinical pharmacology or chemistry). In addition, the sponsor must notify FDA within 5 days of discontinuing a study. Other types of information amendments include transferring the IND to another entity and submitting a change of address.

Safety reports and annual reports must be filed. INDs can also be inactivated, in which case annual reports do not need to be submitted, and reactivated; withdrawn at the sponsor's request; or terminated, if FDA determines that the sponsor is not complying with IND regulations.

More information is available at the following FDA webpages:

- Investigator-Initiated Investigational New Drug (IND) Applications
- Investigational New Drug (IND) Application
- Electronic Regulatory Submission and Review
- Electronic Submissions Gateway

To set up a secure email account, contact SecureEmail@fda.hhs.gov. Nothing that requires a formal decision should be submitted through email.

Helping to End Addiction Long-term® Initiative (NIH HEAL Initiative®) Programs and Funding Opportunities

Eric Hudak, Ph.D., Program Director, Division of Translational Research, National Institute of Neurological Disorders and Stroke

The Helping to End Addiction Long-term® Initiative, or NIH HEAL Initiative®, is an NIH-wide effort to speed scientific solutions to stem the national opioid public health crisis by working on two fronts: understanding, managing, and treating pain and improving prevention and treatment for opioid misuse and addiction. The HEAL Initiative, which has funded more than 1,800 projects since 2018, is a collaboration across NIH Institutes and Centers. More than 300 clinical trials are now underway, and the initiative has active ongoing partnerships with communities; federal, state, and local agencies; private sector companies; and academia.

HEAL's pain research priorities are understanding the biological underpinnings of chronic pain, accelerating the discovery and preclinical development of nonaddictive pain treatments, advancing new nonaddictive pain treatments through the clinical pipeline, and informing best practices for effective pain management while minimizing the risk of addiction.

HEAL's work on pain management includes studies and programs focused on discovery, preclinical development, clinical trials, and implementation. The studies are developing diagnostics, pharmaceuticals, biomarkers, and devices.

HEAL's Translational Devices program aims to support next-generation technologies to diagnose and treat pain by supporting the development, translation, and optimization of safe and effective devices. The program spans the research space, from early device development to clinical trials. Devices are an area of focus for HEAL because they offer precise targeting and little to no risk of addiction.

The devices program has a funding opportunity on development of new devices up to the state of readiness for human testing. The projects are not hypothesis-driven. Another part of the program funds translation, in partnership with the Blueprint MedTech program. This includes access to additional resources to aid in translation and commercialization of the technology.

Another funding opportunity supports research on investigating the mechanisms of pain relief with medical devices. While there are many devices on the market for treating pain, there is not a mechanistic rationale for many of them, and patient responses vary.

The NIH HEAL Initiative also offers SBIR and Small Business Technology Transfer (STTR) funding. Its PURPOSE (Positively Uniting Researchers of Pain to Opine, Synthesize, & Engage) Network is a digital platform to connect pain researchers. It is open to anyone in the research space. Anyone can join at painresearchers.com.

Discussion

Moderator: Andrew Goldstein, M.D., FACOG, IF, Director, The Centers for Vulvovaginal Disorders

Dr. Goldstein asked about the barriers to gynecologic pain research and what solutions participants have found. Dr. Payne said that assessing the menstrual cycle is resource-intensive

and requires a lot of feedback from participants. Her team works with many adolescents and young adults who are already tracking their cycles.

Dr. Goldstein asked what participants were most excited about in the field of gynecologic pain. Dr. Benhabbour said that she was excited about seeing so much great research on gynecologic pain and about the new pipeline of anti-inflammatory drugs. It would be helpful to have approved treatments, rather than the generics that have been used off-label for so long. Mr. Lyon said he is excited about testing a thermal neuromodulation device in animal trials and, later, carrying out clinical trials with a nonpharmacological focus.

Dr. Goldstein asked about barriers to participation for participants. Dr. Bartley said that many women are highly invested in gynecologic pain research and are willing to do anything they can to help, including participate. One major barrier is the time commitment and the burden of reporting on their menstrual cycles. Ms. Kober noted that the use of digital health technologies has made it easier to collect data over time; when tracking was performed by hand, in diaries, so much data were missing that results were sometimes called into question.

Dr. Jeong said that when his team tried a translational study of endometriosis, they found that resources were very limited compared with other areas of study. The methods are also limited, and the field needs basic resources.

Ms. Fleischacker agreed that patients are very interested in helping. She noted that many potential participants in trials are undiagnosed or misdiagnosed, and thus would not know about the opportunity to participate. Those who think their symptoms are normal may not even ask a provider for help. Others may have tried so many treatments that they may be unwilling to add an additional activity in the form of clinical trial participation.

Dr. Bartley said that there is more awareness of endometriosis now than there was five years ago, but many people who come to the clinic have still never heard of it. There needs to be more effort at raising awareness for health care providers, researchers, and women. Dr. Goldstein noted Ms. Batti's moving story about not only the emotional and physical impacts but also the economic difficulty of chronic pain, including the use of treatments that are not approved and therefore may not be eligible for reimbursement by third-party payers.

Dr. Goldstein asked about opioid use in chronic pelvic pain. Dr. Kellogg Spadt said that opioid use is more common among patients with endometriosis than among patients with vulvodynia. In her experience, patients with vulvodynia try to avoid taking opioids and are more willing to use benzodiazepines or diazepam suppositories. Both groups would welcome cannabidiol (CBD)- or tetrahydrocannabinol (THC)-based treatments.

Dr. Goldstein said he had submitted an IND application for a CBD-based suppository to treat pelvic pain, but it seems that companies were unwilling to do the costly preclinical work, because such a product would be difficult to patent. He ultimately withdrew the IND. Ms. Kober suggested collecting data on cannabis use even in studies that are not focused on CBD or THC products. This could be factored in, to help determine whether a product is more effective than a placebo. Mr. Lyon said he heard a similar discussion about psilocybin at a recent NIH HEAL Initiative event.

Dr. Goldstein said that researchers must continue to conduct well-designed clinical trials that account for as many variables as possible, with heterogeneous participants, to help the millions of people who are suffering from gynecologic pain.

Dr. Ahn thanked all attendees and asked anyone who would like to share research findings at the 2025 meeting to email her.