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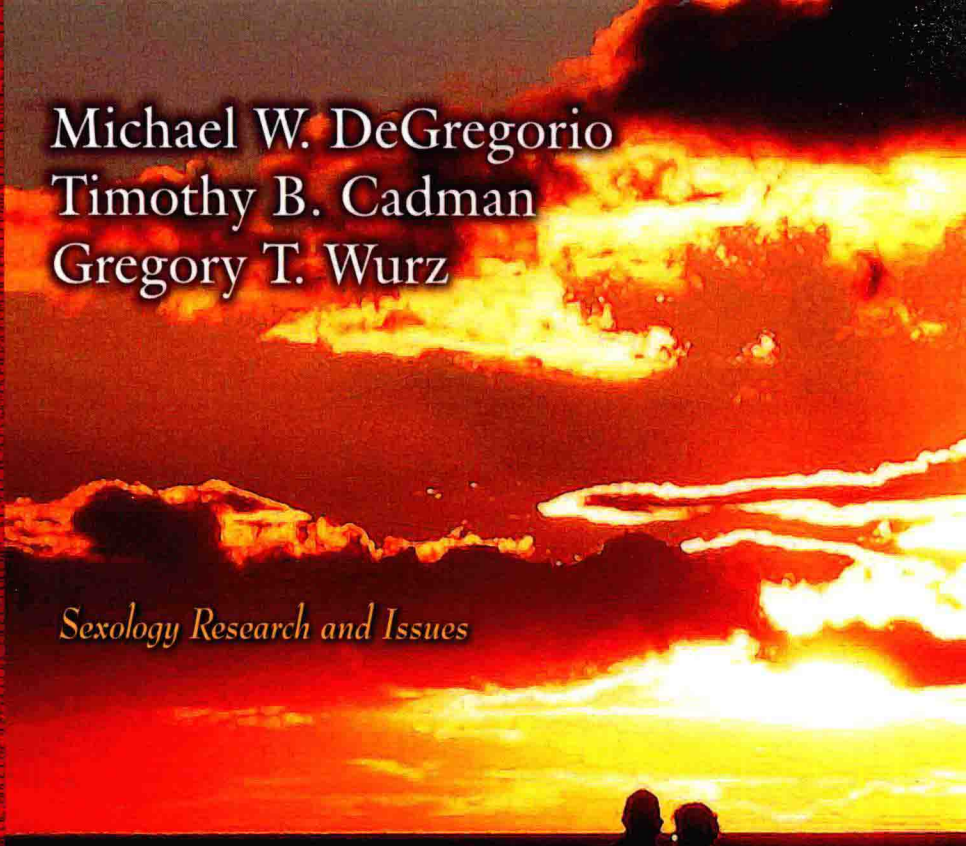

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Sexology Research and Issues

Painful Sex Associated with M[redacted]use

Interpreting FDA Warnings when Choosing a Treatment for Dyspareunia

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SEXOLOGY RESEARCH AND ISSUES

PAINFUL SEX ASSOCIATED WITH MENOPAUSE

INTERPRETING FDA WARNINGS WHEN CHOOSING A TREATMENT FOR DYSPAREUNIA

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About the Authors

Michael W. DeGregorio has been involved in hormonal research since the early 1980s, including the development of toremifene for the treatment of breast cancer, the study of tamoxifen as a chemopreventive agent, and he was a co-inventor of ospemifene for osteoporosis and menopausal symptoms. He has over 100 scientific publications and is co-author of the book *Tamoxifen and Breast Cancer* (Yale University Press, 1994). Dr. DeGregorio is currently a Professor of Medicine at the University of California, Davis in the Department of Internal Medicine, Division of Hematology and Oncology.

Timothy B. Cadman began his career in clinical pharmacology at Yale University in 1988 and later received an M.B.A. from the University of Oregon in 1999. As a student, he was one of the first to develop analytical methodologies for ospemifene while in Dr. DeGregorio's laboratory. During the past 26 years, Mr. Cadman has been instrumental in critical steps along the ospemifene development pathway. Currently, he continues in his role as a strategic leader in furthering the field of hormonal research at the University of California, Davis in the Department of Internal Medicine, Division of Hematology and Oncology.

Gregory T. Wurz received his B.S. from the University of Texas at San Antonio in 1991 and his doctorate in Pharmacology and Toxicology from the University of California, Davis in 2007. He has published over 40 peer-reviewed research articles, many of which examined the pharmacology of ospemifene. His doctoral dissertation explored ospemifene activity as a breast cancer chemopreventive agent. He has

been working with Dr. Michael DeGregorio for 23 years. Dr. Wurz is currently a senior scientist at the University of California, Davis in the Department of Internal Medicine, Division of Hematology and Oncology.

Preface

The most common treatment for menopause-related health issues has been to replace the lost levels of naturally occurring estrogen hormone in a woman's body as she ages. This is called hormone replacement therapy (HRT), and the lead product for this type of treatment is Premarin®, which was first approved for use by the U.S. Food and Drug Administration (FDA) back in 1942. Premarin® is also known as conjugated equine estrogens (CEE) because it is a mixture of estrogens derived from the urine of pregnant horses. Prior to 1962, FDA approval for prescription treatments required merely a demonstration of short-term safety, and thus Premarin® was never subjected to today's rigorous FDA standards, not the least of which requires that all active ingredients of a medication must be defined. Premarin® contains 11 defined compounds and up to 219 additional compounds that have not been defined. Over time, significant health issues have been linked to the long-term use of Premarin® in some patients. Due to increasing concern for public health, the FDA announced in 1997 that approvals for generic forms of Premarin® would no longer be issued.

Dyspareunia is a medical term for painful sexual intercourse that results from vulvar and vaginal atrophy (VVA), which is a common health issue that many women experience during the perimenopausal and postmenopausal stages of life. Until recently, Premarin® had been the only therapy approved by the FDA for the treatment of dyspareunia. In 2013, a new option arrived for women suffering from this health problem. Ospemifene, sold under the trade name Osphena™, is a *non-estrogen* therapy that has been approved by the FDA under today's most rigorous standards. To date, clinical studies have shown that Osphena™ is a safe alternative to Premarin® with fewer risks and more tolerable side effects following short-course (12-week) therapy. While

the long-term impacts of Osphena™ still need to be proven, thousands of women have already benefitted from this treatment over years of carefully controlled clinical trials to ensure that it is safe and effective for postmenopausal women. Even though clinical data suggest that Osphena™ is a safe alternative to Premarin® and other estrogen therapies, the FDA has elected to label Osphena™ with health warnings similar to Premarin®, warnings that we believe to be unjustified based on the available data. Osphena™ contains a single, defined, active ingredient that is a non-estrogen. Premarin® is a mixture of 11 known estrogens and up to 219 other compounds with unclear effects on humans. In our opinion, the risks of Osphena™ cannot practically be considered similar to the risks of Premarin®.

The development of Osphena™ was initially based on a public need for safer alternatives for preventing osteoporosis, breast cancer, and other menopausal health issues. Although Osphena™ currently represents a small step towards the achievement of these lofty goals, further research is ongoing in this field of science. The authors of this book have been involved in the study of women's health issues as far back as the 1980s, and we are continuing with our research to this day. The goal of this book is to educate you specifically concerning options for treating dyspareunia. We attempt to present a balanced discussion of estrogen and non-estrogen therapies, but we expect that some readers might conclude that our opinions are biased due to our involvement in the discovery and development of Osphena™. We believe that it is essential to express our opinions as informed scientists, and wherever possible we also include facts and references so that you may draw your own conclusions or discuss them with your doctor. We chose to present you with a question-and-answer style discussion of dyspareunia, including its impact on quality of life and options for treatment. From discovery through FDA approval and beyond, we provide a history of dyspareunia therapies with an emphasis on Premarin® and Osphena™.

Health warnings are commonly misunderstood, sometimes underappreciated and other times overblown. Today's television commercials for FDA-approved medications can be both confusing and overwhelming. In this book, we take the time to review the latest advertisements for Premarin® and Osphena™, explaining all of the stated contraindications, risks, and side effects of these two treatment options. We also provide an education on "boxed warnings" and walk through "package inserts" which are the fine print warnings that come with every prescription. In addition, we provide an update on the latest scientific results of potential breakthroughs for the prevention of osteoporosis and breast cancer that non-estrogen therapies might offer.

We hope that this book will improve your awareness of dyspareunia, help you understand what treatments are available, and guide you through the process of selecting the best option for yourself.

Michael W. DeGregorio
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Contents

Chapter 1

Quality of Life Impacts of Vulvar and Vaginal Atrophy (VVA) and Other Menopausal Symptoms

Abstract

The menopausal transition is a significant time period in a woman's life, marking the end of her reproductive years. Today, the average woman may live one-third or more of her life in postmenopause. Beginning during the menopausal transition (perimenopause) and continuing into postmenopause, women experience a number of different symptoms such as hot flashes and night sweats, insomnia, vulvar and vaginal atrophy (VVA), vaginal dryness, and painful sexual intercourse, known as dyspareunia, any or all of which can negatively affect their quality of life. Although the menopausal symptoms experienced can vary from woman to woman depending on ethnicity, geographic distribution, body mass and other factors, the most characteristic and problematic symptoms of the menopausal transition are hot flashes, or flushes, and night sweats, which are collectively termed vasomotor symptoms, and they are experienced by up to 80% of menopausal women at some point in their lives. These symptoms are a natural result of the declining sex hormone levels seen in women as they progress through perimenopause and into postmenopause. Unlike vasomotor symptoms, which typically decrease in severity and frequency with time, other postmenopausal conditions like VVA and bone loss, known as osteoporosis, are usually chronic and progressive without treatment. Using a question and answer format, this Chapter provides a discussion of the most commonly

encountered symptoms experienced by women as they enter the menopausal transition, why they occur, and the potentially negative impacts they may have on health and quality of life.

Introduction

With lifespans increasing throughout the developed world, women can be expected to live approximately one-third of their lives after the menopausal transition. A woman is considered to be in menopause, also termed postmenopause, once she has gone 12 consecutive months since her last menstrual period [1]. In the United States, women reach menopause at an average age of approximately 51 years, but ages can range from as young as 38 years up to 55 years [1]. In 2001, the Stages of Reproductive Aging Workshop (STRAW) designed a staging system, since updated in 2011, to classify reproductive aging in women from their reproductive years through postmenopause [2]. The nomenclature and time periods proposed by STRAW as they relate to perimenopause and postmenopause are used here. Prior to menopause, women progress through what is known as the menopausal transition, also known as perimenopause, which is a time period that may last four or more years. During early perimenopause, women continue to experience monthly menstrual periods, but they begin to vary in length by at least seven days in consecutive cycles. In late perimenopause, which can last up to three years, women may experience episodes of amenorrhea, or cessation of menstrual bleeding, lasting 60 days or more. Perimenopause is characterized by fluctuating levels of the sex hormone estrogen [3] and declining levels of the hormones progesterone and testosterone [1]. It is during late perimenopause and early postmenopause that women are most likely to experience hot flashes and night sweats, which are collectively known as vasomotor symptoms (VMS) [4]. Heart palpitations, or a sensation that the heart is racing, can accompany VMS episodes. During this time frame, women may also begin experiencing the symptoms of vulvar and vaginal atrophy (VVA), namely painful sexual intercourse, or dyspareunia, and vaginal dryness, which typically worsen without treatment as women progress into late postmenopause [5].

Common menopausal symptoms experienced by women as they transition from perimenopause and into menopause—vasomotor symptoms, vaginal dryness and dyspareunia, as mentioned—can negatively impact their quality of life. All of these symptoms result from the naturally declining levels of the

female sex hormones estrogen and progesterone as women transition from perimenopause into menopause. While some of these symptoms, such as hot flashes, gradually abate over time, others such as vulvar and vaginal atrophy and osteoporosis, or bone loss, are normally chronic and progressive in some postmenopausal women. It is estimated that as many as 50% of postmenopausal women suffer from vulvar and vaginal atrophy and dyspareunia [6, 7], but many women may be reluctant to seek treatment for these conditions due to cultural and religious differences, social embarrassment or the belief that their symptoms are just a natural consequence of aging that should be accepted [8]. Many women may also simply be unaware that their condition is treatable, and as a result, dyspareunia is often underreported to their doctors [9-11]. Until the early 2000s, the most commonly used remedy to alleviate these symptoms was estrogen replacement therapy in hysterectomized women, or women without a uterus, and hormone replacement therapy (HRT), which contains estrogen combined with the hormone progesterone, in postmenopausal women with a uterus. Following publication of the results of the Heart Estrogen/progestin Replacement Study (HERS) in 1998 [12] and the HERS II [13] and Women's Health Initiative (WHI) estrogen plus progestin trials in 2002 [14], the use of systemic hormone replacement therapy declined markedly [15]. For the treatment of menopausal symptoms such as vulvar and vaginal atrophy in symptomatic women, non-hormonal lubricants and moisturizers and low-dose vaginal estrogen therapy are now the norm [5]. The use of hormone replacement therapy for the treatment of menopausal symptoms and the associated risks are discussed in detail in Chapter 3.

1. What Hormonal Changes Occur During the Menopausal Transition?

Menopause is primarily characterized by a decline in the principal female sex hormone estrogen, also referred to as estradiol. As levels of estrogen begin to fluctuate during perimenopause, many women begin to experience vasomotor symptoms, discussed below. Estrogen levels begin to steadily decline following the last menstrual period, and this can lead to the eventual development of vulvar and vaginal atrophy and osteoporosis (bone loss), which are usually chronic and progressive without treatment. However, changes in other sex hormones also occur during the menopausal transition that can have important consequences. For example, concentrations of

progesterone, sometimes referred to as the "pregnancy hormone" due to high levels seen during pregnancy, steadily decline beginning in perimenopause and continuing into postmenopause. Progesterone deficiency can lead to fluid retention, insomnia and irritability, among other symptoms [1]. The principal male sex hormone, testosterone, is also important in normal female sexual function, and as levels of this hormone steadily decline during the menopausal transition, women may experience decreased sexual libido, reduced muscle strength, depression and anxiety [16]. Testosterone is also important in maintaining bladder and urethral musculature, which is the muscle lining the urethra that carries urine out of the bladder [17]. A number of clinical studies in menopausal women have shown improvements in menopausal symptoms and increased sexual desire and satisfaction with the use of testosterone therapy [18-20]. However, the benefits of using testosterone therapy for the treatment of menopausal systems are still unclear. The importance of testosterone in normal female sexual function has been demonstrated in women who became menopausal through surgery, i.e. removal of the ovaries. Because the ovaries normally produce testosterone, these women experience a sharp, approximately 50% decline in testosterone as a result of the surgery [20], and they are significantly more likely to experience reduced sexual desire compared to naturally menopausal women of the same age [21-23].

2. What Are Vasomotor Symptoms (VMS) and Why Do They Happen?

Vasomotor symptoms, i.e. hot flashes and night sweats, are the most characteristic and problematic symptoms associated with menopause [4], affecting 60-80% of perimenopausal and early postmenopausal women [24]. Vasomotor symptoms are so called because they involve the involuntary dilation and constriction, termed vasodilation and vasoconstriction, of the peripheral vasculature, or blood vessels. The dilation and constriction of these blood vessels occurs through the action of the sympathetic ("fight or flight") branch of the autonomic nervous system on the smooth muscles lining the blood vessels. Relaxation of these muscles leads to vessel dilation and increased blood flow into capillary beds, which results in the "flushing" response and sensation of heat during a hot flash episode. Sweat glands are controlled in the same fashion, and sweating episodes often accompany hot flashes. Occasionally, some women experience heart palpitations (i.e. a sensation that the heart is pounding or racing) in combination with hot flash

and sweating episodes, particularly at night [25]. In some women, vasomotor symptoms can have a profound impact on quality of life. Fortunately, for some women, these symptoms dissipate within several months [26]; however, the median duration of the period during which vasomotor symptoms are experienced is approximately four years [4, 27], and there are some postmenopausal women who continue to experience these symptoms for 20 years or longer [27].

Although the precise mechanism(s) underlying the occurrence of vasomotor symptoms remains unclear, it is thought that the major cause lies in the part of the brain called the hypothalamus [4, 24], which controls the body's core temperature, among many other critical functions. As estrogen levels fluctuate during perimenopause and steadily decline following the last menstrual period, the normal core body temperature range narrows in symptomatic women such that small increases in core body temperature that are normally innocuous can exceed the upper threshold for heat tolerance [4]. In symptomatic women, these small increases in core body temperature can cause the hypothalamus to trigger a hot flash episode in an attempt to dissipate what the brain perceives as excess heat. Sweating often accompanies the hot flash to increase heat dissipation through evaporative cooling. It has been hypothesized that fluctuating levels of estrogen may lead to changes in the amounts of the neurotransmitters norepinephrine and serotonin in the central nervous system (i.e. the brain and spinal cord), which then leads to flushing and sweating episodes [4, 28, 29]. Neurotransmitters are chemical messengers released by neurons, or brain cells, to transmit signals to other neurons. The administration of estrogen is believed to normalize the production of serotonin and norepinephrine, which then restores normal thermoregulation [4].

This hypothesis is supported by research showing that the administration of non-hormonal agents can alleviate vasomotor symptoms while having no effect on estrogen levels [4]. Furthermore, clonidine, a drug that blocks norepinephrine release, has been shown to increase the sweating threshold in women exhibiting vasomotor symptoms [30], thus reducing these symptoms [31, 32], while yohimbine, a chemical that increases norepinephrine levels, causes hot flash episodes [30]. More recent research on clonidine in symptomatic postmenopausal women compared to asymptomatic women proved to be inconclusive due to a large placebo effect [33], and thus the role of norepinephrine in affecting the reactivity of peripheral blood vessels remains unclear. A placebo is a "fake" medicine (e.g. a sugar pill) given to patients during a clinical study for the purpose of evaluating the psychological effect that may occur simply because a patient thinks she is taking a beneficial

medication. Administration of serotonin has generally been shown to have the opposite effect [34, 35]. Interestingly, venlafaxine, a Prozac®-like drug that prevents the re-absorption of serotonin, resulting in increased signaling, causes reduced blood flow to the skin, suggesting that serotonin plays an additional role in the reactions of peripheral blood vessels [36], which is known to be increased in women experiencing vasomotor symptoms. Whether the effects of venlafaxine are mediated centrally (i.e. through the brain) or peripherally (i.e. elsewhere) remains unknown [4]. Paroxetine (Paxil®), another drug that affects the reuptake of serotonin, has also been demonstrated to significantly reduce the incidence of hot flashes [37], which has resulted in the recent FDA approval of low-dose paroxetine for the treatment of moderate to severe hot flashes.

Although vasomotor symptoms affect up to 80% of women at some point in the menopausal transition, not all menopausal women experience these symptoms. It is believed that women who report few or no vasomotor symptom episodes during the menopausal transition have more stable levels of estrogen [1], but there are other factors that can influence the incidence of these symptoms, in addition to racial or ethnic differences. The Study of Women's health Across the Nation (SWAN), which followed 3,302 menopausal women from five different ethnic/racial groups for 10 years, revealed positive associations between vasomotor symptoms and several different genetic, lifestyle and demographic factors, which are discussed in greater detail below. While the significance of these factors varied between the various ethnic/racial groups, the positive associations were common to all groups, meaning that genetics, lifestyle and demographic factors contributed to vasomotor symptoms in all ethnic/racial groups to varying degrees [38]. Despite the involvement of these various factors, the SWAN study showed that menopausal status, the transition to late perimenopause in particular, was the factor most strongly associated with vasomotor symptoms [38].

3. What Triggers Vasomotor Symptom Episodes? Are There Any Risk Factors?

Although vasomotor symptoms can occur at any time, they are often experienced at night. Hot flash episodes can occur spontaneously due to the misperception of excess heat by the brain as discussed above, but they have also been associated with a number of different triggers such as sudden changes in ambient temperature, consumption of caffeinated or alcoholic