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PHARMACOVIGILANCE OF HORMONE REPLACEMENT THERAPY IN MENOPAUSAL WOMEN

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ABSTRACT

Menopause, typically occurring around age 51, brings a range of symptoms such as hot flashes, night sweats, joint pain, and mood disturbances. Hormone replacement therapy (HRT), which combines estrogen and progestogen, is used to alleviate these symptoms and offers benefits like reduced mortality and coronary heart disease risk. However, HRT usage remains low in the US and Europe, highlighting a gap in menopausal care. Genitourinary syndrome of menopause (GSM), characterized by vaginal dryness, dyspareunia, and urinary issues, is often under diagnosed despite its prevalence. HRT can be effective for managing GSM symptoms, with personalized treatment plans tailored to individual patient needs and medical histories. Pharmacovigilance plays a critical role in monitoring the safety and efficacy of HRT, aiming to recognize adverse drug reactions and ensure regulatory compliance. Optimizing estrogen levels through personalized titration is essential for maximizing treatment effectiveness while minimizing risks, particularly for populations like breast cancer survivors who may need alternative therapies. Overall, enhancing awareness and access to varied treatment options is vital for meeting the needs of menopausal patients and improving their quality of life.

KEYWORDS: Menopause, Hormone Replacement Therapy (HRT), Genitourinary Syndrome of Menopause (GSM), Pharmacovigilance, Personalized Treatment.

INTRODUCTION

Pharmacovigilance

Definition

Pharmacovigiloance is the study of recognizing, assessing, understanding, and and preventing any negative effects or other drug-related problems are referred to as pharmaceutical surveillance. Monitoring the effects of medications, particularly after they have been put, is its primary goal on the market, to guarantee their efficacy and safety. Using pharmacovigilance can help monitoring known negative effects, discovering ones that had not yet been discovered, and verifying that the benefits of drugs out-weight.

Goals of Pharmacovigilance

Pharmacovigilance Primary Goals are

1. One way to identify adverse drug reactions (ADRs) is to: Recognizing and recording possible hazards connected to pharmaceutical drugs, especially unforeseen consequences or adverse effects.
2. Drug Safety Monitoring: Ensuring continued oversight of pharmaceuticals once they are prescribed market, particularly when it's widely utilized by many demographics.
3. Preventing Harm: Reducing the possibility of patients suffering from drug-related harm by recognizing and addressing safety concerns as soon as possible. Improving Drug Use: Giving regulatory agencies and medical experts information to encourage the efficient and safe administration of drugs.
4. Regulatory Compliance: Ensuring that drug manufacturers follow safety oversight regulations established by regulatory bodies.
5. Encouraging Public Health: By guaranteeing the safety and efficacy of pharmacological therapy, Pharmacovigilance contributes to the enhancement of general public health results.
6. After-Market Surveillance: Observation.

Menopause: What Is It?

After a year of amenorrhea due to the irreversible loss of ovarian function, menopause is identified. Menopause occurs at an average age of 51 years. The last menses occur several months before the per menopause, a period of altered ovarian activity years. There is uncertainty regarding the physiology and clinical signs of this menopausal transition. Recognized; yet, certain symptoms, including hot flushes, unquestionably start in the the per

menopause. It's critical to acknowledge the significance that different women place on different aspects of health Results from hormone replacement treatment can vary.

Therefore, each woman should decide whether to utilize hormone replacement treatment in concert with the other. And her healthcare provider, following thorough evaluation of potential advantages, hazards, and her individual.

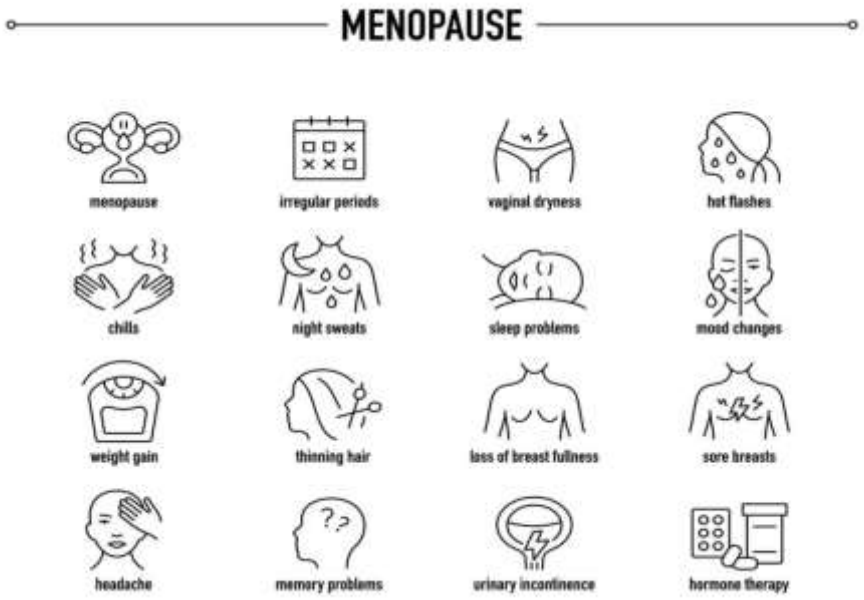

Figure No 01: Symptoms of Menopause.

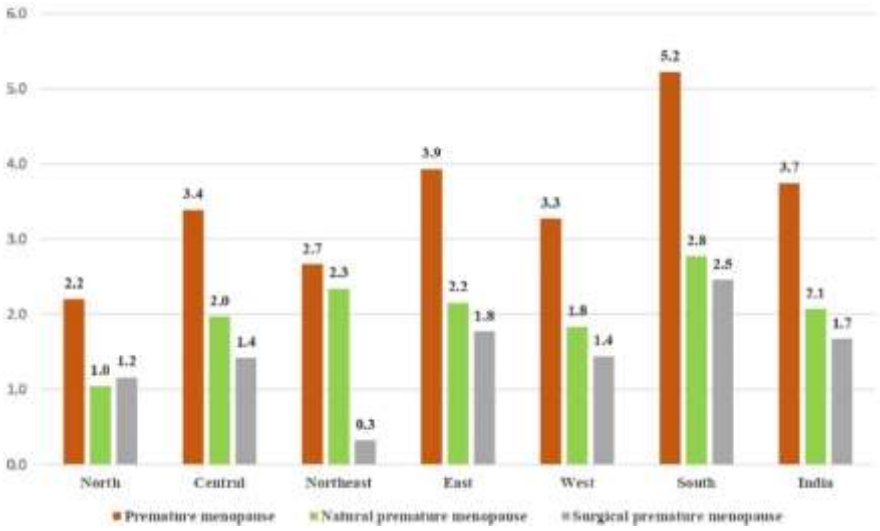

Figure No 02: Graphical representation of menopause.

What is Hormone Replacement Therapy?

Menopause is a typical physiological occurrence that affects women at the median age of 51. Hormone replacement therapy (HRT) relieves menopausal symptoms and protects the endometrium in women who are still in their uterus by combining estrogen and progestogen. The estrogen can be used orally, topically, or intravaginally. It may also be conjugated equine estrogen, oestrone, oestradiol 17β, or oestradiol. According to Mirena and Bayer Schering, the progestogen can be given orally, transdermally, or intrauterinally. In HRT regimens, progesterone can be introduced gradually (cyclic regimen) or constantly (continuous combined regimen) to oestrogen, which is taken daily. An oral synthetic steroid formulation with oestrogenic, androgenic, and progestogenic properties, tibolone serves as a HRT agent.

Key Points

1. The topic of hormone replacement therapy (HRT) has generated a lot of debate.
2. Observational research has already shown that HRT has many benefits, such as a reduction in mortality and coronary heart disease (CHD).
3. Research including randomized treatment of elder women (over 60) revealed no benefit and increased hazard. It is necessary to review clinical trials for women beginning treatment close to menopause because new studies and meta-analyses have identified rare risks as well as advantages.
4. The benefits of estrogen alone over estrogen + progesterone are further supported by research.
5. HRT may have a primary preventative role, as evidenced by the benefits of reduced CHD and mortality in women beginning treatment around menopause.

The last menstrual cycle and the decline in ovarian follicular function characterize the physiological condition known as menopause. This causes a notable decrease in estrogen secretion, which has varying effects on each woman's quality of life and associated health concerns. During the menopause transition and the first several years after menopause, bothersome climacteric symptoms are fairly common. Hot flashes and night sweats are the most common of these, although other symptoms including joint pain or the genitourinary syndrome of menopause (GSM) are also commonly reported, as are sleep and mood issues. Although these symptoms can last for years after the onset of menopause, the prevalence of these symptoms and their impact on quality of life vary among postmenopausal women.

Additionally, there are t has been suggested that the study's features restrict the findings' applicability to all postmenopausal women, despite the fact that the WHI is still the only sizable, long-term randomized controlled trial of postmenopausal women utilizing MHT. Consequently, MHT is linked to a favorable benefit-risk balance in early postmenopausal women within the first ten years following menopause or before the age of sixty, according to statements from the International Menopause Society. However, the majority of US and European nations still utilize MHT at relatively low rates 20 years after the WHI. This is especially true in France, however it's unclear what proportion of postmenopausal women are receiving MHT at the moment. This calls into question how menopause is managed and whether menopausal patients have unmet needs.

OBJECTIVES

- To evaluate how menopause-related and genitourinary symptoms are being managed in France, with a particular emphasis on the use of menopause hormone treatment (MHT).
- Participants, environment, and design A population-based survey of 5004 representative French women between the ages of 50 and 65 is known as the ELISA Study.
- The women who took part in the study completed a computer-assisted web interview in July and August of 2020 regarding menopause-related and genitourinary symptoms, as well as how to treat them, including using MHT.

Historical Background

- 03 November 2016In the original published article, reference 41 was incorrect.
- The correct reference is Carrasquilla, G. D. et al.
- The association between menopausal hormone therapy and coronary heart disease depends on timing of initiation in relation to menopause onset: results based on pooled individual participant data from the Combined Cohorts of Menopausal Women — Studies of Register Based Health Outcomes in Relation to Hormonal Drugs (COMPREHEND) study [abstract S17]. Menopause 22, 1373 (2015**).**
- This error has been corrected in the HTML and PDF versions of the article.

Stages of Trials

- Patient 1 is a 52-year-old woman at average risk for breast cancer and osteoporosis who is having menopause-related hot flashes and disturbed sleep.
- Patient 2 is a 58-year-old woman with osteopenia whose mother had breast cancer.

- Patient 3 is a 65-year-old woman with a history of coronary revascularization and documented osteoporosis. Each wants to know whether hormone-replacement therapyis right for her

Management

In order to address each category of symptoms individually, distinct treatments are available.

1. **Areas Covered:** Numerous treatments exist for VMS, such as hormonal therapy using estrogen and progestins, as well as a novel option called tissue-selective estrogen complex (TSEC), tibolone, phytoestrogens, and progestins alone. Additionally, data supports the usefulness of selective serotonin reuptake medications. There are other nonhormonal options available as second-line therapies, although their efficacy is still unclear. Nonhormonal therapies for the GSM include vaginal lubricants and moisturizers; further research is needed to support the use of vaginal lasers as an option. Conversely, hormonal therapy including systemic or local estrogen are an option. The most successful treatments include TSEC and the most recent selective estrogen receptor modulator (SERM), ospemifene. Studies are still being conducted on testosterone and dehydroepiandrosterone (DHEA) therapies. Nonhormonal therapies for the GSM include vaginal lubricants and moisturizers; further research is needed to support the use of vaginal lasers. Conversely, hormonal therapies including systemic or local estrogen are an option. The most successful treatments include TSEC and ospemifene, the most recent SERM. Studies on testosterone and DHEA therapies are ongoing.
2. **Expert Opinion:** We have more options now that there are more therapies available for menopausal symptoms, but we still need to customize care. Patients who previously had no options now have choices, which can increase compliance. It's also critical to develop treatment plans that use combined or sequential therapies.

Modern Management of Genitourinary Syndrome of Menopause

The established term for the wide range of symptoms and indicators associated with these changes is genitourinary syndrome of menopause (GSM)2. Table 1 summarizes the typical clinical symptoms. According to reports, 50–70% of postmenopausal women have some degree of GSM symptoms; nonetheless, despite its significant prevalence, GSM is still incredibly under diagnosed.

Table 1: Clinical features of genitourinary syndrome of menopause.

	Genital	Sexual	Urinary
Symptoms	• Vaginal dryness (most common & troublesome) • Itching/burning/irritation • Vaginal/pelvic pain and pressure	• Dyspareunia • Reduced lubrication • Loss of libido/arousal • Post-coital bleeding	• Dysuria • Urgency • Stress/urgency incontinence • Urinary tract infections • Urinary frequency/nocturia
Signs	• Labial atrophy • Decreased moisture • Loss of vaginal rugae • Vaginal pallor • Decreased elasticity • Higher vaginal pH level • Leukorrhea • Introital stenosis • Pelvic organ prolapse • Thinning/greying pubic hair		• Urethral prolapse/caruncle • Ischaemia of vesical trigone • Meatal stenosis

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Procedure of Hormone Replacement Therapy in Menopause

Menopause patients undergoing hormone replacement treatment (HRT) may take progestin, estrogen, or a mix of the two. The needs and medical history of the patient determine the kind of HRT and how it is administered.

1. Hormone treatment may be ingested as a tablet, ring, skin patch, gel, cream, or spray. Taking a larger dose of estrogen that is absorbed throughout the body is known as systemic estrogen therapy. Urinary and vaginal symptoms are treated with low-dose vaginal estrogen formulations.
2. Estrogen and progesterone can be administered together. There are two methods that women who still have uteruses can mix progestin and estrogen.
3. Daily administration of combination therapy: progestin and estrogen are administered together.
4. Cyclical therapy: Progestin is given for 10 to 14 days per month in addition to estrogen, which is taken daily.

5. Substances Injected certain medications used in hormone therapy can be injected into the arm, leg, hip, or just beneath the abdominal area.

Clinical Benefits and Side Effects of HRT

The current doses of estrogen have demonstrated therapeutic benefits, but they also carry a risk of causing clinical side effects that could lead to non-compliance and reduced efficacy. It is commonly believed that the least likely time to suffer any cyclic discomfort is during the mid-follicular phase of a typical menstrual cycle, when plasma E2 is still between 60 and 150 pg/ml. The incidence of pregnancy-like symptoms, such as bloating, breast tenderness, and mood swings, tends to grow after E2 climbs to 150 pg/ml in the mid-luteal Conversely, asthenia, sleep issues, depression, headaches, and migraines are more common during perimenstrual days when E2 drops to 40 pg/ml or lower.

Therefore, studies on postmenopausal women and castrated animals show that plasma E2 levels of about 100 pg/ml are optimal for managing hot flashes, halting bone loss, and safeguarding the heart. Because of the large interindividual variation in estrogen clearance rate, it is unlikely that any standardized unique dose of oral or non-oral formulations will reproduce the optimal levels in all postmenopausal users.

To improve true efficacy and long-term compliance, individual titration efforts are necessary. Because older postmenopausal women generally have a better clinical tolerance to low E2 levels, objective indicators of effectiveness should also be established when the purpose of hormone replacement treatment (HRT) is to avoid osteoporosis or vascular diseases. unfavorable consequences linked to various metabolic and clinical conditions.

Who Should Not Take Menopausal Hormone Therapy?

Because some research indicates that MHT may raise the chance of breast cancer recurrence, women who have previously experienced breast cancer are frequently advised to avoid it. Other research, meanwhile, hasn't revealed a higher risk. For instance, there was no higher risk of death or recurrence linked to the administration of systemic or vaginal MHT in a Danish cohort analysis of postmenopausal women treated for early-stage breast cancer phas Many studies have also been done to investigate whether MHT is safe for women who haveexperienced premature or severe menopausal symptoms as a result of cancer treatments thatreduce hormone levels. A 2020 clinical practice statement from the Society of Gynecologic Oncology concluded that the benefits of MHT are likely to outweigh the risks

for most peoplewith epithelial ovarian, early-stage endometrial, and cervical cancer as well as for people withBRCA1 or BRCA2 gene mutations or Lynch syndrome and no history of breast cancer. However, the statement recommended against the use of MHT in women with advanced endometrial cancer, uterine sarcoma, or endometrioid or low-grade serous ovarian cancer.

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